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Protein Complexes that Modify Chromatin

With 38 Figures and 5 Tables

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Cover Illustration:

Dividing Drosophila S2 cell (metaphase). The chromosomes are stained in green with an antibody against the Drosophila MYST-type histone acetyltransferase dMoz. dMoz is the fly homologue of the human candidate proto-oncoprotein Monocytic Leukemia Zinc Finger. The mitotic spindle appears in red (labeled with antibodies against acetylated alpha-tubulin; Sigma, St. Louis, MO). Courtesy of Dr. Thomas Kusch, Howard Hughes Medical Institute, PennState University.

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Preface

An early view of eukaryotic chromosomes was that of static structures, which stored DNA not in use within a given cell type. It was thought that packaging of DNA into higher levels of chromatin structure would suffice to repress gene expression and that the challenge to the cell would be to rescue specific sequences from these structures. The extensive packaging of inactive DNA was considered the primary difference between eukaryotic and prokaryotic genomes and except for that point both would be similarly regulated by cis-acting sequences and trans-acting factors. Our view of eukaryotic chromosomes has evolved dramatically over the last decade. The picture of chromosomes that is emerging is that of dynamic breathing organelles actively regulating the flow of genetic information from the genome. Indeed chromatin is so fluid that even maintaining gene quiescence is an active process and is tightly regulated. Chromatin dynamics is a consequence of protein complexes that modify histones, remove histone modifications, mobilize nucleosomes or stabilize nucleosomes. A wide variety of such complexes have now been described. Some are abundant and may play global roles in chromosome fluidity and function. Others are more rare and specialized for specific functions at discreet loci. Moreover, several complexes share biochemical activities and genetic studies suggest overlapping functions in vivo. Many components of these complexes were first revealed in genetic screens, while others were discovered by novel cell biological or biochemical approaches.

This volume of *Current Topics in Microbiology and Immunology* reviews a wide variety of protein complexes that modify chromatin. We begin by describing protein complexes that assemble nucleosomes and chromatin structures. Nucleosomes are not spontaneously formed upon the addition of histones to DNA. Instead the histone octamer must be assembled onto the DNA. As described by Ito, this involves a fine-tuned process whereby histone chaperones (e.g., NAP1, ASF1,

CAC1) donate histones in an ordered process during nucleosome assembly. Nucleosome spacing is achieved by the action of ATP-dependent nucleosome remodeling complexes (e.g., ACF, CHRAC) that can move histone octamers along DNA in cis. This process can be reversed. ATP-dependent chromatin remodeling complexes can move nucleosomes out of the way of other DNA-binding proteins and histone chaperones can participate in nucleosome disassembly. Nucleosome assembly complexes also play an important role in the formation of more specialized chromatin structures. The chapter by SHARP and KAUFMAN describes the assembly and function of centromeres and centromeric heterochromatin. In this process, a specialized histone variant is assembled into the nucleosome arrays. As noted above, the formation and propagation of silenced heterochromatin is an active process carried out by histone-modifying enzymes (methylases and deacetylases) and a number of protein complexes that recognize these histone marks. KELLUM describes the proteins involved in heterochromatin formation and maintenance and the role of nuclear architecture/location in its function. One of the proteins binding heterochromatin is HP1. HP1 also associates with cohesin a protein complex required for sister chromatid cohesion at centromeres. Cohesin and condensin, a protein complex required for mitotic chromosome condensation, contain SMC (Structural Maintenance of Chromosomes) ATP-driven motor proteins. YOKOMORI describes the functions of the SMC proteins in the maintenance of chromosome integrity. YOKOMORI, KAUFMAN and KELLUM all note the potential role of SMC proteins in heterochromatin function.

A number of chromatin-modifying complexes have more direct roles in regulating gene expression. The chapters by VERRIJZER and colleagues and by WANG describe the prototype ATP-dependent chromatin remodeling complex, SWI/SNF. SWI/SNF complexes are larger and less abundant than their more distant relatives (e.g., ACF, CHRAC). However, these complexes play important roles in the developmental control of gene expression. As described by VERRIJZER, SWI/SNF complexes oppose the repressive action of polycomb complexes during *Drosophila* development. WANG describes how in humans SWI/SNF complexes also play important roles as tumor suppressors. The abundant SPN or FACT complex binds directly to nucleosomes and is thought to alter nucleosome structure as described by FORMOSA. This activity of the SPN complex appears to play a critical role in the elongation of RNA

polymerase and perhaps DNA polymerase through nucleosomes. SPN also appears to recruit additional protein complexes to chromatin as part of its function. Histone acetylation has been linked to gene activity for several decades. UTLEY and COTE review one class of enzymes responsible for this modification, the MYST family of histone acetyltransferase proteins. Each of these enzymes is found in a multiprotein complex and has been implicated in processes as diverse as gene activation, gene silencing, X-chromosome dosage compensation and DNA repair. Histone deacetylation is as tightly regulated as histone acetylation. The function of nuclear hormone receptors provides a prime example of this regulation as these complexes often bind histone acetyltransferase co-activator complexes in the presence of their ligands but instead bind histone deacetylase co-repressor complexes in the absence of ligands. JONES and SHI describe the nuclear co-repressor proteins, N-CoR and SMART, which are found in several complexes associated with histone deacetylase activities. FENG and ZHANG describe another histone deacetylase complex, NuRD. The NuRD complex contains both a histone deacetylase enzyme and ATP-dependent chromatin remodeling activity, thus, linking these two processes. NuRD has been found to be part of the MeCP1 complex, which illustrates an important role of NuRD in methylated DNA-based gene silencing.

These chapters nicely illustrate the diversity and complexity of protein complexes that utilize chromatin as substrates while regulating several genomic processes. I thank all the authors for their time and effort in preparing these chapters and Ms. Lorene Stitzer for assisting in assembling the text. I hope you enjoy reading this volume of *Current Topics in Microbiology and Immunology* and take from it a deeper impression of the dynamics of eukaryotic chromatin.

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August 2002

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List of Contributors

(Their addresses can be found at the beginning of their respective chapters.)