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Introduction: assembly, remodeling and modification of chromatin

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Research on eukaryotic chromatin has undergone a dramatic transition in the past ten years. While once considered as a mostly static and inert material with a function in DNA packaging and transcriptional repression, chromatin is now recognized as a dynamic and interactive structure that is assembled, remodeled and modified in response to cellular signaling. Rearrangements of chromatin structure are of essential importance in regulating gene expression and other nuclear processes, such as DNA replication, recombination and repair, but also cell cycle progression and developmental transitions.

The basic repeating unit of chromatin is the nucleosome, a protein octamer of core histones (an H4/H3 tetramer and two H2A/H2B dimers) around which usually 146 bp DNA are wrapped. While 20 years ago the nucleosome was thought to serve as a means of packaging DNA into a relatively small cell nucleus, it is now clear that nucleosomal structure exerts regulatory functions which we are beginning to understand. The core histones form the core octamer of the nucleosome by protein-protein interactions of their globular domains; crystallographic analysis revealed that the free N-terminal tails of the core histones protrude from the core octamer [1]. The flexible N-terminal extensions contain conserved amino acid residues that are subject to various posttranslational modifications; the most prominent of these modifications is acetylation, where an acetyl group of acetyl coenzyme A is linked to the ε-amino group of lysine by histone acetyltransferases (HATs) and may be removed by histone deacetylases (HDACs). A number of gene regulatory proteins have been identified as HATs or HDACs, or have been shown to act in complexes with such enzymes.

This multi-author review aims to present an overview on the mechanisms involved in the dynamic transitions of chromatin structure. The articles summarize the current knowledge on chromatin assembly, remodeling and modification, with special emphasis on histone acetylation; it has become evident that these processes do not function independently from each other but are part of a complex, interdependent regulatory network. Protein complexes that assemble and relocate nucleosomes, alter the structural properties of nucleosomes and acetylate nucleosomal histones are well characterized to date.

During DNA replication histones must be deposited onto newly replicated DNA by the aid of chromatin assembly factors, and the further organization of nucleosomes is facilitated by the ATP-dependent chromatin assembly and spacing factor. The review by Krude and Keller discusses nucleosome assembly pathways with a focus on how this process is linked to DNA replication and the cell cycle [2]. Exciting new connections are emerging between nucleosome assembly proteins (NAPs) and transcriptional coactivators with HAT activity. It has recently been demonstrated that NAP 1 and 2 interact with -p300/CBP; this interaction is modulated by core histones [3], suggesting that NAP can serve as a bridging protein between transcriptional coactivators and chromatin. Chromatin remodeling complexes can basically be distinguished into two categories: complexes dependent on ATP hydrolysis and complexes that utilize HAT or HDAC activity. The review of Havas et al. deals with the class of ATP-dependent chromatin remodeling activities [4]; there is increasing evidence for a coordinated action of ATP-dependent remodeling complexes and chromatin-modifying complexes. The composition of high molecular weight, multiprotein complexes of mammalian cells containing HAT activity is summarized by Ogryzko; in addition to their roles for activation or repression of gene activity, these complexes are discussed with respect to their possible roles for epigenetic inheritance [5]. The HAT component of the multiprotein complexes has been the subject of detailed structural analyses during the past three years. Marmorstein reviews the structure of different HATs, namely Gcn5/PCAF, Esa1 and Hat1 [6]. These structural and functional studies provide a framework for understanding the mode of enzymatic catalysis and the mode of histone binding.

Since the identification of HATs and HDACs as transcriptional regulators and coregulators [7, 8], histone

acetylation moved into the center of current research interest, in particular the field of gene regulation. Multiple HAT and HDAC families have been described, and there seems hardly any chromatin-associated process in which HATs or HDACs are not involved. Most of these results have been obtained in yeast and animal cells. However, plants contain HDAC-types unrelated to known HDACs from yeast or animals. Graessle et al. review the current data on histone acetylation, especially on HDACs, in plants and fungi [9]. In addition, filamentous fungi are interesting model systems since *Cochliobolus carbonum,* a plant pathogenic fungus, possesses HDAC activity which is extremly resistant against a variety of HDAC inhibitors. Experimental work with another filamentous fungus, *Neurospora crassa,* provided evidence that histone acetylation can directly or indirectly influence DNA methylation. Dobosy and Selker summarize available data on the DNA methylation – histone acetylation – chromatin remodeling connection [10]. It has recently been shown that CpG methylation represses transcription at the level of RNA polymerase initiation by a mechanism that involves a change in the local histone acetylation pattern; this repression is dominant over a remodeled (demethylated, hyperacetylated) enhancer and does not require large area changes in chromatin structure [11]. Therefore, a localized hypoacetylation as a result of CpG methylation may be sufficient for repression.

The transcriptional silencing by the coordinated action of methyltransferases and HDACs is likely to be involved in tumor formation as well, as outlined in the review of Timmermann et al. [12]. It has been substantiated during the past few years that aberrant chromatin acetylation patterns may cause diverse diseases Specific inhibitors of HDACs and HATs are promising substances for transcription therapy in cancer treatment.

The past decade has revolutionized our understanding of eukaryotic chromatin and transcription in a chromatin environment. This multi-author review presents a state of the art for some aspects of chromatin research. We are just at the cusp of understanding the complex influence of chromatin components on a variety of cellular processes.

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