CHAPTER 2

CHROMATIN MECHANISMS REGULATING GENE EXPRESSION IN HEALTH AND DISEASE

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Abstract: It is now well established that the interplay of sequence-specific DNA binding proteins with chromatin components and the subsequent expression of differential genetic programs is the major determinant of developmental decisions. The last years have seen an explosion of basic research that has significantly enhanced our understanding of the basic principles of gene expression control. While many questions are still open, we are now at the stage where we can exploit this knowledge to address questions of how deregulated gene expression and aberrant chromatin programming contributes to disease processes. This chapter will give a basic introduction into the principles of epigenetics and the determinants of chromatin structure and will discuss the molecular mechanisms of aberrant gene regulation in blood cell diseases, such as inflammation and leukemia.

INTRODUCTION

The range of diseases found to have an epigenetic component responsible for aberrant gene regulation is steadily increasing and diseases of blood cells represent some of the best-defined models for studying this type of dysregulation. Many factors control the growth, differentiation and activation status of blood cells and when these are dysregulated the result can be either leukemia with aberrant growth and differentiation, or autoimmune and inflammatory diseases where the immune system is chronically active.

In this chapter we will introduce the basic concepts of chromatin structure and the processes that control gene expression by modifying chromatin. We will draw upon
examples from both our own work and the work of others to illustrate the role that chromatin and DNA modifications play in normal gene regulation and in blood cell disease. To introduce some of these concepts we will also discuss the consequences of the reprogramming of the transcriptional regulatory network in leukemic cells that result in abnormal patterns of epigenetic modifications within chromatin.

**THE ROLE OF TRANSCRIPTION FACTORS AND CHROMATIN STRUCTURE IN ESTABLISHING PATTERNS OF GENE EXPRESSION**

Gene expression programs are established during cell differentiation by the concerted actions of sets of transcription factors specific to each cell type and to their state of differentiation and activation. Transcription factors perform multiple functions: they recognize a specific DNA sequence, interact with other transcription factors binding to neighboring DNA-sequences or even several kilobases away, respond to extracellular signals and most importantly, recruit nonDNA-binding factor complexes that cooperate to either maintain the active state, or initiate the establishment of an inactive state. These factors, in turn, exert their effects largely at the level of chromatin structure by creating permissive or nonpermissive states. The genome exists naturally in a repressed state by virtue of the fact that regulatory and coding DNA sequences are for the most part occluded by nucleosomes which assemble into highly condensed and inaccessible structures. Before a gene can be expressed, it is necessary to first create accessible sites for the binding of transcription factors required for transcription initiation and secondly, to modify the histones within nucleosomes and reorganize the higher order chromatin structure to create an environment permissive for the passage of RNA polymerases.

Gene expression programs are typically controlled by transcription factors that are expressed in a temporal sequence during differentiation. Factors such as RUNX1, GATA-2 and PU.1 play pivotal roles in enabling early stages in blood cell differentiation, whereas other factors are responsible for the differentiation of specific hematopoietic lineages. Regulators of differentiation are exemplified by factors such as GATA-3, T-bet and FoxP3 which play important roles in maintaining the balance between effector and regulatory T cells. Other specific classes of transcription factors only become transcriptional activators as a result of external signals. This is true for inducible factors such as NFAT, AP-1 and NF-κB that play essential roles in mediating responses to immune stimuli. Both the developmentally regulated and the inducible classes of transcription factors can contribute to an aberrantly active immune system.

In addition to exerting transient inducible effects, transcription factors can also introduce stably maintained chromatin alterations. In some cases, transcription factors can establish an imprint within chromatin, creating a memory of a previous stimulatory event which persists after inducible transcription has ceased. For example, we and others have evidence that immune or pro-inflammatory stimuli can induce the formation of modified chromatin structures that can persist many cell cycles after the stimulus is withdrawn and which can remain as long-lived imprints in memory T cells for example. Alternatively, specific developmentally regulated transcription factors such as RUNX1 can initiate a cascade of events that become self-perpetuating during blood cell differentiation even after the subsequent removal of the differentiation initiating factor.