

Preface

THE STRUCTURAL STATE OF CHROMATIN, consisting of genomic DNA and its associated proteins, influences all DNA-templated processes, including transcription, replication, and repair. A vibrant area of discovery over the last several decades has been in revealing the repertoire of chromatin components, which includes the enzymes that covalently modify histones and DNA, the ATP-dependent remodelers of nucleosome structure, and the core histone variants that establish specialized chromatin domains. Because these basic chromatin components are ancestral to eukaryotic life, their study in model organisms has led to a deep understanding of roles that they play in mediating gene expression and chromosome integrity. Other chromatin components, especially sequence-specific DNA-binding proteins, drive development by activating or repressing transcription and altering the chromatin landscape to maintain cell-type identity during cell division.

Although mutation or aberrant expression of particular sequence-specific transcription factors has long been known to drive oncogenesis, only in the past several years have we come to appreciate the surprising involvement of chromatin regulators in cancer progression. This sea change can be largely attributed to cancer genome sequencing initiatives, which have revealed that loss- and gain-of-function mutations of genes encoding chromatin regulators are pervasive events in human oncogenesis. In contrast to the well-known oncogenes and tumor suppressor genes that were discovered and studied because of their cancer phenotypes, most chromatin oncoproteins were already very familiar from earlier genetic and biochemical studies. Thus, the study of chromatin deregulation in cancer has greatly profited from decades of research into basic mechanisms of gene regulation and development.

The impetus for this volume is the rapid expansion in our understanding in recent years of how perturbations of chromatin can result in the pathogenesis of human cancer. The major implication of this research is that many of the tumor-specific changes in DNA or histone methylation, which might have been previously interpreted as an epigenetic phenomena, are in fact the direct consequence of mutational changes in genes that encode chromatin regulators. Even histone genes themselves are found mutated in human tumors, a truly compelling example in which chromatin deregulation directly causes cancer. Based on these recently discovered paradigms, most of the chapters of this book are devoted to the chromatin regulatory machineries that are commonly mutated in human cancer and to our current understanding of underlying mechanisms. Other chapters are focused on the area of therapeutic modulation of chromatin, a field of study that has been invigorated by a new generation of small molecules that target chromatin reader, writer, and eraser functionalities. It is our hope that assembling this new body of knowledge in one volume will be of particular use to scientists just entering the chromatin field, as they seek to address the many unanswered questions that remain.

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