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Adam R. Karpf *Editor*

Epigenetic Alterations in Oncogenesis

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Epigenetic Alterations in Oncogenesis

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Preface

Epigenetics refers to heritable changes in gene expression or genome function encoded by marks other than DNA base sequence; information literally “above” the level of genetics. Epigenetic marks include cytosine methylation and cytosine hydroxymethylation, histone tail modifications, histone variants, and nucleosome positional information, all of which are resident along the DNA duplex. Epigenetic marks frequently show interdependent relationships, for example, the close association of DNA methylation states with particular histone tail modifications and histone variants. From the standpoint of cell physiology, epigenetics provides a mechanism for cells to integrate environmental or intrinsic stimuli into heritable changes in genome function. From the standpoint of development, epigenetics provides a platform for cell differentiation and cell specialization, which in principle cannot simply be the consequence of DNA sequence. Most relevant to this book is the fact that changes in epigenetic states are now recognized to play a fundamental role in cancer development and progression. Cancer, almost uniquely among common human diseases, is characterized by natural selection for cellular variants with improved fitness, e.g., proliferative capacity and rate, evasion of cell death, invasive growth, migration to and proliferation at secondary sites, chemotherapy resistance, and a myriad of other naturally or artificially selected phenotypes. Epigenetic changes play a key role in this phenotypic selection, possibly to an equal to or even greater extent than do genetic mutations.

As a field, cancer epigenetics has now reached young adulthood. The observations that started the field were of DNA hypomethylation changes in cancer in the 1980s, followed by the discovery of DNA hypermethylation in cancer in the 1990s. In the last decade, additional alterations at other levels of epigenetic control (e.g., histone modifications) have also been discovered and characterized in cancer. Also, over the past few years rapid progress has been made in translating the findings of epigenetic alterations into new cancer biomarkers and therapeutic targets. One clear highlight in the field has been the FDA-approval of DNA methyltransferase (DNMT) inhibitors and histone deacetylase (HDAC) inhibitors to treat a select number of human malignancies.

The early work in cancer epigenetics was largely hypothesis or “candidate-gene” driven. More recent work using unbiased and global approaches (i.e., epigenomics)

have validated and greatly extended the early observations. Evidence now suggests that DNA hypomethylation is linked to oncogenic gene activation and genomic instability, and that DNA hypermethylation leads to tumor suppressor gene inactivation, including inactivation of DNA repair genes that also may promote genomic instability. Thus, epigenetic mutations (epimutations) appear to promote genetic mutations and genomic rearrangements in cancer. Intriguingly, a number of recent findings largely from cancer genome sequencing data suggest that genes involved in epigenetic control processes are commonly mutated in a variety of cancers, thus demonstrating that genetic changes can also promote epigenetic alterations in cancer. Taken together, the data now indicate that the roles of genetics and epigenetics in cancer development are highly intertwined.

Epigenetic Alterations in Oncogenesis comprises 15 chapters contributed by leading active researchers in the field. The book is divided into three sections that run the gamut from a description of the basic epigenetic mechanisms that regulate gene expression in human cancer, to how alterations in epigenetic marks contribute to cancer biology, and concluding with an account of the uses for epigenetic-targeted drugs to treat human cancer, as well as the analysis methods to decipher cancer epigenomes.

Part I, *Epigenetic Marks and Mechanisms*, provides an introduction to the major epigenetic marks and how these are altered during oncogenesis. The part begins with a discussion by Jin and Robertson in Chap. 1 on cytosine DNMTs and DNA hypermethylation in cancer, and focuses particularly on the silencing of genes involved in DNA repair, which are a frequent target of hypermethylation. In addition, the authors summarize important recent work showing that DNMTs themselves participate in DNA repair processes. In Chap. 2, Ehrlich and Lacey turn attention to the flip side of the coin, DNA hypomethylation, which was the original epigenetic alteration observed in cancer. The authors discuss the diverse genomic contexts in which DNA hypomethylation can occur and present possible mechanisms to explain DNA hypomethylation in cancer. An exciting recent development in epigenetics is the discovery of 5-hydroxymethylcytosine (5-hmC) as a novel epigenetic mark, which itself appears to be linked to DNA hypomethylation. The biological significance of 5-hmC as well as the enzymes that catalyze its formation (ten–eleven translocation or TET proteins, which can be mutated in cancer) is discussed by Kinney and Pradhan in Chap. 3. In Chap. 4, attention turns to altered histone modifications in cancer with a detailed discussion by Campbell and Turner on how posttranslational histone modifications are controlled under normal circumstances and the mechanisms driving their alteration in malignancy. A critical concept in epigenetics is that DNA methylation and histone modifications ultimately impact gene expression and genome function via their effects on nucleosomes; the important topic of altered nucleosome occupancy in cancer is covered by Andreu-Vieyra and Liang in Chap. 5.

Part III, *The Impact of Epigenetic Alterations on Cancer Biology*, discusses how epigenetic changes contribute to critically important cancer phenotypes. The section begins in Chap. 6, where Fabbri and colleagues discuss miRNA expression alterations in cancer caused by epigenetic changes, including DNA methylation, histone modifications, and Polycomb proteins. The importance of this concept is illustrated by the inherent capacity of altered miRNA expression to derange entire

transcriptional programs in cancer cells. A large family of genes known as cancer-testis or cancer-germ line genes encodes antigens that are a major target of cancer vaccines. Additionally, a number of these genes have emerging oncogenic functions. In Chap. 7, De Smet and Loriot discuss how epigenetic mechanisms, most prominently DNA hypomethylation, lead to the activation of these genes in many human malignancies. Andersen and Jones follow this with a discussion in Chap. 8 of how DNA methylation controls cell fate in the intestine and how, when the tumor suppressor gene adenomatous polyposis coli (APC) is lost, this promotes DNA hypomethylation and intestinal tumorigenesis. In Chap. 9, Futscher describes how tractable cell model systems are being used to discern the temporal epigenetic alterations that are linked to cell immortalization and transformation. It is now recognized that epigenetic regulation lies at the heart of stem cell maintenance and differentiation. In Chap. 10, Huang and colleagues discuss epigenetic regulation of mesenchymal stem cells (MSC) during tumorigenesis, and highlight recent work showing that targeted DNA methylation of tumor suppressor genes provides a model system to study MSC-driven tumorigenesis.

Part III, *Clinical Implications and Analysis Methods*, provides an overview of important topics related to the utility of epigenetic alterations as cancer biomarkers and therapeutic targets, and provides a detailed overview of the methods used to decipher cancer epigenomes. In the past few years, a major link between environmental toxicants, epigenetic changes, and cancer has become apparent. In Chap. 11, Pogrinby and Rusyn discuss these developments as they pertain to chemical carcinogens such as arsenic, as well as other pharmaceutical and biological agents. While epigenetic alterations in cancer cells and tumor tissues is well established, emerging data suggest that systemic epigenetic changes (i.e., those affecting normal tissues) can also occur in cancer patients, as well as in individuals with elevated risk for cancer. Marsit and Christensen highlight the current research in this exciting and potentially high impact area in Chap. 12. Epigenetic therapies have entered the clinic and received their first widespread use in the context of myeloid malignancies, particularly myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML). In Chap. 13, Griffiths and Gore discuss the clinical work in this arena, with a focus on the FDA-approved azanucleosides 5-azacytidine (vidaza) and decitabine (dacogen), but also touching on HDAC inhibitors. In Chap. 14, Balch and Nephew discuss how epigenetic therapies may be particularly well suited for chemotherapy sensitization to overcome drug resistance, and review the extensive preclinical work and rapidly accumulating clinical knowledge in this area. Finally, in Chap. 15, Costello and colleagues review the approaches used for the analysis of cancer epigenomes. In particular, they discuss the methods appropriate for the analysis of cytosine methylation and hydroxymethylation, discuss next-generation sequencing approaches, and touch on the computational methods now being used to explore cancer epigenomes.

Acknowledgments

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