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Editorial

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Decades of research have revealed the complexity of transcriptional regulation. DNA sequence elements, transcription factors, and chromatin structure contribute to the transcriptional output of the genome. C.H. Waddington first coined the term “epigenetic landscape” in 1942 as a conceptual framework to describe interactions between genetic elements and the environment. Today, “Epigenetics” has evolved into a discipline centered on defining heritable changes in gene expression that are transmitted from one generation to the next without alterations in DNA sequence. Epigenetic phenomena involve methylation of DNA sequences and post-translational modifications of chromatin proteins. These marks serve as a layer of information added to the underlying DNA sequences that govern the heritable transcription status of a gene. Recent studies have demonstrated the importance of epigenetics in normal growth and development. To emphasize the impact of epigenetics, we assembled this Special Issue of *Mutation Research-Fundamental and Molecular Mechanisms of Mutagenesis* areas of expertise.

The review articles within this issue discuss a wide range of epigenetic modifications, with several emphasizing modifications of histones. A contemporary framework for thinking about epigenetic histone modifications is provided by C.D. Allis and colleagues. These authors describe a “histone code” that involves writers, readers and erasers. Combinatorial post-translational modifications, mostly on histone tails, make up the code. Writers are enzymes that generate post-translational modifications predominantly on histone tails. Readers are proteins possessing domains that recognize particular post-translational histone modifications. Erasers are enzymes that remove the epigenetic marks, providing the ability to reverse the transcriptional status of a gene. Several articles in this issue focus on the readers and writers. C.D. Allis and colleagues discuss proteins possessing PHD domains that function as readers of the code. Mutations in genes encoding these proteins are associated with human disease, possibly due to misinterpretation of the code. L.L. Wallrath and colleagues focus on the chromo domain protein Heterochromatin Protein 1, a code reader that plays a role in chromatin packaging and gene regulation. Down-regulation of HP1 is associated with progression of many types of cancer, implying that failure to read the code causes misregulation of gene expression and cancer progression. J.A. Simon and C.A. Lange demonstrate a connection between a code writer, EZH2, and cancer. EXH2 is the catalytic subunit of a Polycomb complex that methylates histone tails, causing developmentally regulated gene repression. Over-

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expression of EZH2 is associated with a variety of cancer types, suggesting that ectopic placement of the code is problematic.

The histone code is coordinated with DNA methylation. Several articles within this issue describe connections between histone modifications and DNA methylation in association with gene silencing. The interplay of epigenetic modifications is a focus of the article by K.D. Robertson and colleagues. Connections between DNA methylation and histone methylation, as they relate to mammalian development and human disease, are discussed. P. Wade and colleagues describe a family of proteins that bind methylated DNA in a manner analogous to the readers of the histone code. In general, these proteins recruit histone modifiers and silence gene expression. The methyl DNA binding protein MeCP2 is discussed in detail as mutations in the gene encoding this protein give rise to a major form of mental retardation. The function of MeCP2 has been extremely elusive over the years, with new data suggesting a role in forming higher order chromatin structures.

The reversible nature of epigenetic modifications provides the opportunity for therapeutic intervention of human disease. P.A. Jones and colleagues deliver hopeful news regarding “epigenetic drugs” that impact DNA methylation and histone modifications. Some of these drugs have proven success in the treatment of hematological malignancies and certain types of solid tumors. The authors acknowledge shortcomings of such drug treatments and suggest means of improvement.

Embryonic stem cells provide a promising source of therapy for degenerative diseases. These cells self-renew in culture and can differentiate into nearly all cell lineages within an organism. Maintenance of their pluripotential state is under epigenetic control. H.-H. Ng, Y.-H. Loh and colleagues highlight the cross-talk between transcriptional circuitry and epigenetic mechanisms in embryonic stem cells. Changes in gene expression that accompany lineage commitment, differentiation and proliferation are associated with alterations in chromatin structure that involve the redistribution of nucleosomes. ATP-dependent chromatin remodeling machines are responsible for shifts in nucleosome positions. R.H. Seong and colleagues discuss the role of chromatin remodeling complexes, with emphasis on embryonic and hematopoietic development.

Developmental model systems have provided a wealth of information connecting gene regulation with epigenetic mechanisms. Two of the best studied examples are described in articles provided by the laboratories of A. Dean and M. Bartolomei. A. Dean and colleagues discuss developmental expression of the *β globin* locus that involves long-distance epigenetic regulation and genomic insulator elements. M. Bartolomei and colleagues describe the epigenetics of the *H19/Igf2* segregation. J.L. Gerton and colleagues bring to light new roles for cohesions in gene expression. A second class of new epigenetic regulators includes nuclear envelope proteins. E. Schirmer discusses “laminoapthies”, a collection of diseases associated with mutations in genes encoding nuclear envelope proteins. Such proteins provide structural support for the nucleus and make connections with chromatin, thereby organizing the genome in three dimensions. Proximity of a gene to the nuclear envelope has consequences on gene expression. Therefore, defects in envelope proteins are anticipated to alter organization within the nucleus, causing misregulation of gene expression.

In sum, this Special Issue contains review articles that describe the complexities of transcriptional control by interconnected epigenetic modifications of DNA and chromatin. Defects that disrupt epigenetic marks cause developmental disorders and disease. Fortunately, the reversible nature of epigenetic marks makes therapy possible. New therapies will rely on the identification of additional factors involved in epigenetic modifications and a better understanding of the mechanisms that regulate transcription.