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Protein Complexes that Modify Chromatin **Protein Complexes that Modify Chromatin** **Protein Complexes that Modify Chromatin** **Chromatin Regulation and Dynamics** **Molecular Biology of the Cell** Chromatin Dynamics in the DNA Damage Response Introduction to Genetics *Developmental Gene Regulation by Chromatin Modification Factor MpE(z) and Its Target Genes KNOX and BELL in the Basal Land Plant Marchantia Polymorpha* Epigenetics Protocols **Epigenetic Mechanisms of Gene Regulation** Epigenetic Technological Applications *The Role of Lysine Methylation in Disease Pathogenesis* **Epigenetic Gene Expression and Regulation** Centromere **RNA-directed Chromatin Modification in Arabidopsis Thaliana** *Current Frontiers and Perspectives in Cell Biology* **Chromatin** Nutrients and Epigenetics *Chromatin Architecture Chromatin and Epigenetics* **Maintenance of Open Chromatin States by Histone H3 Eviction and H2A.Z** *The Molecular Relationship Between Chromatin-reading Modules and Combinatorial Histone Modifications* **Protein Complexes that Modify Chromatin Epigenetics: Development and Disease A Prion Epigenetic Switch Drives Inheritance of an Activated Chromatin State Natural Genetic Variation Involved in Chromatin Modification Current trends in Bioinformatics: An Insight** Mechanisms of Lymphocyte Activation and Immune Regulation XI *Epigenetics and Chromatin: Advanced Concepts of Cell Biology Investigating the Role of Histone Modifications in Stable Differentiation and Reprogramming in the Arabidopsis Stomatal Lineage* **Chromatin Remodelling** *Recent Advances of Epigenetics in Crop Biotechnology Expression of Histone Modifying Proteins and Chromatin Remodelling Factors in Swine Oocytes and Developing Embryos Site-directed insertion of transgenes* *Current Topics in Tropical Emerging Diseases and Travel Medicine* **bHLH Transcription Factors in Development and Disease Centromere Mechanisms and Novel Therapies in Graves' Orbitopathy: Current Update Introduction to Epigenetics** Current Topics in Developmental Biology

The post-genomic era has brought new challenges and opportunities in all fields of the biology. In this context, several genome engineering technologies have emerged that will help deciphering genes function by as well as improve gene therapy strategies. Genomic modifications such as knock-in, knock-out, knock-down, sequence replacement or modification can today be routinely performed. However, in front of this large palette of methodologies scientists may experience difficulties to gather useful information's scattered within the literature. This book aims to present the state of this field from basic mechanisms of site-directed modifications to their applications in a wide range of organisms such as bacteria, yeast, plants, insects, mammals. It will discuss the problems encountered when using the random integration strategy and present the recent advances made in targeted genome modification. Technologies based on Zinc Finger nucleases, Meganucleases, TALEN, CRE and FLP recombinase, □C31 integrase, transposases and resolvases are fully detailed with their strengths and weaknesses. All these information's will help students and experienced researchers to understand and choose the best technology for their own purposes. DNA methylation is the modification of DNA molecule, transferring methy group to the 5th position of the cytosine pyrimidine ring. This biochemical process plays a crucial role in many cellular processes of higher organisms. For example, people have found distinct patterns of

DNA methylation during cellular differentiation and tissue development. The differential DNA methylation profiles are often associated with gene expression. In addition, DNA methylation reveals genomic imprinting and affects on chromatin remodeling and cellular homeostasis. Such epigenetic modification has also been proven to be involved in nearly all cancer-related signaling pathways. However, the mechanism and process against how DNA methylation regulates gene expression are still not clear. The study of DNA methylation and its regulation on gene expression provides fundamental and new insights into the genetic heritability. In Chapter 1, Gene duplication event of NAC transcription factor genes in rice and Arabidopsis was analyzed, then it was found that chromosomal segment duplications mainly contributed to the expansion of both species, whereas tandem duplication occurred less frequently in Arabidopsis than rice. Chapter 2 reviews the current literature related to the epigenetics of alcoholism and summarizes our advanced study of global DNA methylation in human post-mortem frontal cortex tissues obtained from adult alcoholics and controls utilizing new microarray technology and bioinformatics approaches. Chapter 3 gives a comprehensive synopsis over the epigenetic modifications involved in the regulation of bacterial gene expression as well as the patho-epigenetic modifications in eukaryotic host tissues triggered in the pathogenesis of particular Gram-negative bacterial infections. Both, basic molecular mechanisms and complex pathogenetic relations are described. Chapter 4 provides an epigenetic repressing mechanism for breast cancer metastasis by recruiting NuRD complex to ESR1 gene through TWIST1. Chapter 5 summarises most of mouse models that have helped us better understand the pathogenesis mechanism during the development of colitis. In Chapter 6, the authors review the various forms of presentation of celiac disease including the lymphocytic enteritis, along with their systemic manifestations. Chapter 7 provides an insight to inflammatory response in light of DNA regulation and methylation of key players. Because chronic inflammatory diseases do share common features, recent progress in our understanding of renal fibrosis and inflammation in chronic kidney disease will be discussed as an example of epigenetic regulation in inflammatory diseases. Chapter 8 summarizes the regulation of gene expression in pterygium. Pterygium is an ocular surface disease and its pathogenesis is currently unknown. Here, the genetic and epigenetic changes in the disease are explored. Chapter 9 summaries the basics and applications of recently proposed MiRaGE method that infer miRNA-mediated regulation of target genes and miRNA-targeting-specific promoter methylation. The applications to differentiation, cell senescence, and miRNA transfection to lung cancer celll lines are discussed. Chapter 10 proposes the role of AP-1 chromatin modulator Jun dimerization protein 2 (JDP2) on antioxidant response and inhibition of ROS production via Nrf2-ARE signaling, as well as the induction of replicative senescence. Chapter 11 compares expression profiles of mRNAs, microRNAs and proteins of human embryonic stem cells hES-T3 grown on different feeders and conditioned media. Chapter 12 reviews the most recent molecular markers of Amyotrophic Lateral Sclerosis (ALS) and shows some innovative perspectives on this topic from the point of view of gene therapy. In addition, non-viral gene therapy based on the non-toxic C-terminal fragment of the tetanus toxin (TTC) will also be discussed. A numerous internationally renowned authors in the pages of this book present the views of the fields of cell biology and their own research results or review of current knowledge. Chapters are divided into five sections that are dedicated to cell structures and functions, genetic material, regulatory mechanisms, cellular biomedicine and new methods in cell biology. Multidisciplinary and often quite versatile approach by many authors have imposed restrictions of this classification, so it is certain that many chapters could belong to the other sections of this book. The current frontiers, on the manner in which they described in the book, can be a good inspiration to many readers for further improving, and perspectives which are highlighted can be seen in many areas of fundamental biology, biomedicine, biotechnology and other applications of knowledge of cell biology. The book will be very useful for beginners to gain insight into new area, as well as experts to find new facts and

expanding horizons. The term "chromatin remodelling" is widely used to describe changes in chromatin structure which is controlled by histone-modifying enzymes, chromatin remodelling complexes, non-histone DNA-binding proteins and noncoding RNAs. Many human diseases such as cancer, various genetic syndromes, autism and infectious disease have been linked to the disruption of these control processes by genetic, environmental or microbial factors. Therefore, to unravel the mechanisms by which they operate is one of the most exciting and rapid developing fields of modern biology and will contribute to new ways in treatment of these diseases. The chapters in this book will focus on recent advances in our understanding of the mechanisms that govern the dynamic structural of chromatin, thereby providing important insights into gene regulation, DNA repair, and human diseases. Epigenetic Technological Applications is a compilation of state-of-the-art technologies involved in epigenetic research. Epigenetics is an exciting new field of biology research, and many technologies are invented and developed specifically for epigenetics study. With chapters covering the latest developments in crystallography, computational modeling, the uses of histones, and more, Epigenetic Technological Applications addresses the question of how these new ideas, procedures, and innovations can be applied to current epigenetics research, and how they can keep pushing discovery forward and beyond the epigenetic realm. Discusses technologies that are critical for epigenetic research and application Includes epigenetic applications for state-of-the-art technologies Contains a global perspective on the future of epigenetics Tropical emerging diseases pose a significant risk for the circulation of old and new pathogens in areas previously unknown, also implying the possibility of new morbidities and mortalities and new consequences for naïve populations. Globalization, migration and travel are key factors for tropical diseases, and represent the need for integration of tropical medicine, travel medicine and epidemiology in the understanding of such complex situations. Neglected tropical diseases such as leprosy or Chagas disease, arboviral diseases, HIV, Ebola, and arenaviral infections are just a few examples. This book tries to update significant epidemiological and clinical research in many aspects with a multinational perspective. An early view of eukaryotic chromosomes was that of static structures, which stored DNA not in use within a given cell type. It was thought that packaging of DNA into higher levels of chromatin structure would suffice to repress gene expression and that the challenge to the cell would be to rescue specific sequences from these structures. The exten sive packaging of inactive DNA was considered the primary difference between eukaryotic and prokaryotic genomes and except for that point both would be similarly regulated by cis-acting sequences and trans acting factors. Our view of eukaryotic chromosomes has evolved dra matically over the last decade. The picture of chromosomes that is emerging is that of dynamic breathing organelles actively regulating the flow of genetic information from the genome. Indeed chromatin is so fluid that even maintaining gene quiescence is an active process and is tightly regulated. Chromatin dynamics is a consequence of protein complexes that modify histones, remove histone modifications, mobi lize nucleosomes or stabilize nucleosomes. Awide variety of such com plexes have now been described. Some are abundant and may play glo bal roles in chromosome fluidity and function. Others are more rare and specialized for specific functions at discreet loci. Moreover, several complexes share biochemical activities and genetic studies suggest overlapping functions in vivo. Many components of these complexes were first revealed in genetic screens, while others were discovered by novel cell biological or biochemical approaches. Epigenetics is a new field that explains gene expression at the chromatin structure and organization level. Three principal epigenetic mechanisms are known and hundreds of combinations among them can develop different phenotypic characteristics. DNA methylation, histone modifications and small RNAs have been identified, and their functions are being studied in order to understand the mechanisms of interaction and regulation among the different biological processes in plants. Although, fundamental epigenetic mechanisms in crop plants are beginning to be elucidated, the

comprehension of the different epigenetic mechanisms, by which plant gene regulation and phenotype are modified, is a major topic to develop in the near future in order to increase crop productivity. Thus, the importance of epigenetics in improving crop productivity is undoubtedly growing. Current research on epigenetics suggest that DNA methylation, histone modifications and small RNAs are involved in almost every aspect of plant life including agronomically important traits such as flowering time, fruit development, responses to environmental factors, defense response and plant growth. The aim of this Research Topic is to explore the recent advances concerning the role of epigenetics in crop biotechnology, as well as to enhance and promote interactions among high quality researchers from different disciplines such as genetics, cell biology, pathology, microbiology, and evolutionary biology in order to join forces and decipher the epigenetic mechanisms in crop productivity. The field of epigenetics has grown exponentially in the past decade, and a steady flow of exciting discoveries in this area has served to move it to the forefront of molecular biology. Although epigenetics may previously have been considered a peripheral science, recent advances have shown considerable progress in unraveling the many mysteries of nontraditional genetic processes. Given the fast pace of epigenetic discoveries and the groundbreaking nature of these developments, a thorough treatment of the methods in the area seems timely and appropriate and is the goal of Epigenetics Protocols. The scope of epigenetics is vast, and an exhaustive analysis of all of the techniques employed by investigators would be unrealistic. However, this TM volume of Methods in Molecular Biology covers three main areas that should be of greatest interest to epigenetics investigators: (1) techniques related to analysis of chromatin remodeling, such as histone acetylation and methylation; (2) methods in newly developed and especially promising areas of epigenetics such as telomere position effects, quantitative epigenetics, and ADP ribosylation; and (3) an updated analysis of techniques involving DNA methylation and its role in the modification, as well as the maintenance, of chromatin structure.

Epigenetics is the study of heritable changes in gene expression that occur independent of changes in the primary DNA sequence. Chromatin structure defines the state in which genetic information is organized in the cell. The organization of this structure greatly influences the abilities of genes to be activated or silenced. In eukaryotic cells, 146 base pairs of DNA is wrapped around the histone octamer (two H2A/H2B dimers and one H3/H4 tetramer) forming the nucleosomes, the basic unit of chromatin. The nucleosome cores are connected by linker DNA sequences to further package into higher-order chromatin structures. In addition to the core histones, each histone contains an unstructured N-terminal tail. The histone tails are the sites of most of the post-translational modifications (PTMs), such as acetylation, methylation and phosphorylation. These modifications regulate the structure and function of chromatin through two general mechanisms. In the first model, histone modifications may play a direct role in altering chromatin structure. For example, histone acetylation neutralizes the positive charge of lysine residues and thus, affecting the interactions of the histones with DNA, transcription factors and other nucleosomes. Secondly, histone modifications can indirectly affect chromatin functions by serving as a binding platform for modular proteins and complexes. For instance, the methylation of histone H3 at lysine 9 is recognized specifically by the chromatin organization modifier (Chromo) domain of heterochromatin protein 1 (HP1), which contributes to the induction and the propagation of heterochromatin structure. Ten years ago, Strahl and Allis proposed a general idea of "histone code" hypothesis, which states that histone modifications, distinct or in combination, to form a "code" to influence chromatin structure and lead to varied transcriptional outputs. In recent years, many chromatin regulators were identified, such as the proteins that "write" or "erase" or "read" the modifications. Some chromatin regulators are expressed in a tissue-specific manner and play important roles in physiology and disease pathogenesis. For instance, the H3K27 histone methyltransferase EZH2 is overexpressed in tumors such as prostate, breast, colon, skin and

lung cancer. Disruption of normal patterns of covalent histone modifications is another hallmark of cancer. One of the most characterized examples is the global reduction of the trimethylation of H4K20 and acetylation of H4K16, along with hypomethylation, at repeat sequences in many tumors. Since post-translational modifications have been shown to be important for many biological processes such as gene expression, DNA damage and repair and apoptosis, disruption of these processes has been linked to carcinogenesis and other disease pathogenesis. The discovery of reversible mutations in the epigenetic machinery makes post-translational modifications as one of the most promising and expanding fields in the current biomedical research. Methylation does not neutralize the charge of the modified residue nor does addition of methyl groups add considerable bulk, this mark is believed to create a distinct molecular architecture on histones that is recognized by specialized binding domains present within chromatin-regulatory proteins. The proteins and domains that recognize histone modifications, named "effectors" or "readers", are thought to define the functional consequences of lysine methylation by transducing molecular events at chromatin into biological outcomes. Mutations in these "readers" proteins have been shown to link to many disease pathogenesis. However, relatively few effector domains have been identified in comparison to the number of modifications present on histones and non-histone proteins. Here we developed a human epigenome peptide microarray platform (HEMP) for high-throughput discovery of chromatin effectors. We probed this platform with modification-specific antibodies and known chromatin effector domains to test the integrity of the peptides on the slides. We also screened a library of Royal Domain family members and identified three effector proteins with novel modified-histone binding activity. Hence, the development of the HEMP facilitates the identification of effector proteins and understanding of chromatin signaling networks. Multiple Myeloma (MM) is a malignancy of bone marrow plasma cells that frequently results in bone marrow destruction, bone marrow failure and death. 15% of patients with multiple myeloma is diagnosed with an immunoglobin gene, t(4; 14), translocation. MM patients carrying the t(4; 14) translocation is associated with the overexpression of WHSC1/MMSET/NSD2. NSD2 is a protein lysine methylatransferase in the nuclear receptor binding SET domain protein family. However, the molecular mechanism by which NSD2 contributes to myeloma pathogenesis is not known. Here we show that the dimethylation of histone H3 at lysine 36 (H3K36) is the principal physiological activity of NSD2. In mammalian cells, H3K36me2 normally maps to gene bodies. In t(4; 14)+ myeloma cells, overexpression of NSD2 disrupts the physiologic genomic organization of H3K36me2 which is found being dispersed throughout the genome. NSD2 expression is linked to transcription activation and H3K36me2 location at gene bodies positively correlates with transcription levels. In Myeloma cells, NSD2-mediated localized elevation of H3K36me2 induces transcription at normally inert cancer-associated genes. Catalytic activity of NSD2 confers tumor formation in xenograft model and promotes oncogenic transformation of primary cells by regulating transcriptional programs that favor oncogenesis. The BAH domain is an evolutionarily conserved chromatin-associated motif. Utilizing the HEMP, we screened several BAH domains from yeast and human for binding activity. We found that the BAH domain of human ORC1 specifically bind to H4K20me2 peptides. Structural studies show that BAH domain has an aromatic dimethyl-lysine-binding cage that interacts with the bound peptide. ORC1 is dispensable for ORC complex assembly but is necessary for loading of the complex into chromatin. The ability of ORC1 BAH domain binding to H4K20me2 is required for the efficient stabilization of ORC complex at chromatin. H4K20me2 is enriched at replication origins. Abrogation in ORC1 and H4K20me2 interactions impairs cell-cycle progression. Mutations in ORC1 BAH domain have been implicated in aetiology of Meier-Gorlin syndrome (MGS), a form of primordial dwarfism. In a zebrafish model, orc1 morphants display an MGS-like dwarfism phenotype, which can be rescued by wild type Orc1 but not ORC1 binding mutants. Zebrafish depleted with H4K20me2

also displays the MGS-like phenotype. Together, our findings reveal a new function for histone methylation signaling at chromatin in the regulation of DNA replication and organismal growth. KDM2A is the first jumonjiC domain-containing demethylase identified. We solved the co-crystal structure of KDM2A and its substrate, H3K36me2. We found that KDM2A demethylation activity is required to maintain genomic stability. We also show that KDM2A is a tumor suppressor and its demethylation activity is required for suppressing cellular transformation. Many inheritable changes in gene function are not explained by changes in the DNA sequence. Such epigenetic mechanisms are known to influence gene function in most complex organisms and include effects such as transposon function, chromosome imprinting, yeast mating type switching and telomeric silencing. In recent years, epigenetic effects have become a major focus of research activity. This monograph, edited by three well-known biologists from different specialties, is the first to review and synthesize what is known about these effects across all species, particularly from a molecular perspective, and will be of interest to everyone in the fields of molecular biology and genetics. Epigenetics fine-tunes the life processes dictated by DNA sequences, but also kick-starts pathophysiological processes including diabetes, AIDS and cancer. This volume tracks the latest research on epigenetics, including work on new-generation therapeutics. An early view of eukaryotic chromosomes was that of static structures, which stored DNA not in use within a given cell type. It was thought that packaging of DNA into higher levels of chromatin structure would suffice to repress gene expression and that the challenge to the cell would be to rescue specific sequences from these structures. The exten sive packaging of inactive DNA was considered the primary difference between eukaryotic and prokaryotic genomes and except for that point both would be similarly regulated by cis-acting sequences and trans acting factors. Our view of eukaryotic chromosomes has evolved dra matically over the last decade. The picture of chromosomes that is emerging is that of dynamic breathing organelles actively regulating the flow of genetic information from the genome. Indeed chromatin is so fluid that even maintaining gene quiescence is an active process and is tightly regulated. Chromatin dynamics is a consequence of protein complexes that modify histones, remove histone modifications, mobi lize nucleosomes or stabilize nucleosomes. Awide variety of such com plexes have now been described. Some are abundant and may play glo bal roles in chromosome fluidity and function. Others are more rare and specialized for specific functions at discreet loci. Moreover, several complexes share biochemical activities and genetic studies suggest overlapping functions in vivo. Many components of these complexes were first revealed in genetic screens, while others were discovered by novel cell biological or biochemical approaches. Chromatin Regulation and Dynamics integrates knowledge on the dynamic regulation of primary chromatin fiber with the 3D nuclear architecture, then connects related processes to circadian regulation of cellular metabolic states, representing a paradigm of adaptation to environmental changes. The final chapters discuss the many ways chromatin dynamics can synergize to fundamentally contribute to the development of complex diseases. Chromatin dynamics, which is strategically positioned at the gene-environment interface, is at the core of disease development. As such, Chromatin Regulation and Dynamics, part of the Translational Epigenetics series, facilitates the flow of information between research areas such as chromatin regulation, developmental biology, and epidemiology by focusing on recent findings of the fast-moving field of chromatin regulation. Presents and discusses novel principles of chromatin regulation and dynamics with a cross-disciplinary perspective Promotes crosstalk between basic sciences and their applications in medicine Provides a framework for future studies on complex diseases by integrating various aspects of chromatin biology with cellular metabolic states, with an emphasis on the dynamic nature of chromatin and stochastic principles Integrates knowledge on the dynamic regulation of primary chromatin fiber with 3D nuclear architecture, then connects related processes to circadian regulation of cellular metabolic states, representing a paradigm of adaptation to environmental changes In recent

years, major developments have increased understanding of various genetic and epigenetic regulatory processes that are critical for the generation of B cell repertoires. These include the role of chromatin regulation and nuclear organization in understating the IgH gene regulation. These proceedings highlight recent developments in lymphocyte development, Ig gene rearrangements and somatic hypermutation, chromatin structure modification, B lymphocyte signaling and fate, receptor editing, and autoimmunity. The centromere is a chromosomal region that enables the accurate segregation of chromosomes during mitosis and meiosis. It holds sister chromatids together, and through its centromere DNA–protein complex known as the kinetochore binds spindle microtubules to bring about accurate chromosome movements. Despite this conserved function, centromeres exhibit dramatic difference in structure, size, and complexity. Extensive studies on centromeric DNA revealed its rapid evolution resulting often in significant difference even among closely related species. Such a plasticity of centromeric DNA could be explained by epigenetic c- trol of centromere function, which does not depend absolutely on primary DNA sequence. According to epigenetic centromere concept, which is thoroughly d- cussed by Tanya Panchenko and Ben Black in Chap. 1 of this book, centromere activation or inactivation might be caused by modifications of chromatin. Such acquired chromatin epigenetic modifications are then inherited from one cell di- sion to the next. Concerning centromere-specific chromatin modification, it is now evident that all centromeres contain a centromere specific histone H3 variant, CenH3, which replaces histone H3 in centromeric nucleosomes and provides a structural basis that epigenetically defines centromere and differentiates it from the surrounding chromatin. Recent insights into the CenH3 presented in this chapter add important mechanistic understanding of how centromere identity is initially established and subsequently maintained in every cell cycle. This book sheds new light on the current state of knowledge concerning chromatin organization. Particular emphasis is given to the new imaging potential offered by super-resolution microscopy, which allows DNA imaging with a very high labeling density. From the early work on chromosomes by Walther Flemming in the nineteenth century to recent advances in genomics, the history of chromatin research now spans more than a century. The various milestones, such as the discovery of the double helix structure, the sequencing of the human genome, and the recent description of the genome in 3D space, show that understanding chromatin and chromosome function requires a clear understanding of its structure. Presenting cutting-edge data from super-resolution single molecule microscopy, the book demonstrates that chromatin manifests several levels of folding, from nucleosomes to chromosomes. Chromatin domains emerge as a new fundamental building block of chromatin architecture, with functions possibly related to gene regulation. A detailed description of chromatin folding in the pachytene stage of meiosis serves as a model for exploring this functionality, showing the apparent interplay between structure, function, and epigenetic regulation. Lastly, the book discusses possible new avenues of innovation to describe chromatin’s organization and functions. Gathering essential insights on chromatin architecture, the book offers students an introduction to microscopy and its application to chromatin organization, while also providing advanced readers with new ideas for future research. This new volume of Current Topics in Developmental Biology provides a comprehensive set of reviews on bHLH transcription factors. bHLH factors are vastly recognized for their diverse roles in developmental processes and their dysfunction underlies various human pathologies. Each chapter is authoritatively written by a leading expert in the field and discusses every possible aspect of this huge and diverse field. Covers the area of basic helix-loop-helix (bHLH) transcription factors in development and disease International board of authors Provides a comprehensive set of reviews on our current understanding on the function of bHLH factors in development of various tissues and how de-regulation of these factors can cause, or is linked to, various human diseases The enormous amount of genomic information encoded within

our DNA is dynamically regulated by epigenetic mechanisms, to allow different interpretation of the same DNA blueprint. The post-translational modifications (PTMs) of histones are major components of epigenetic mechanisms and have a direct regulatory role in chromatin-dependent processes, such as transcription, DNA replication and DNA repair. Histone modification is also tightly associated with genetics and metabolism, through which it is linked to environment sensing and normal development. The action of histone modifications is mediated by histone-reading modules (reader domains), which are small protein modules that recognize specific histone modifications. Histone-reading modules are often part of large chromatin-modifying complexes, and mediate important biological outputs via the specific interaction with histone PTMs. Over the last decade, people have identified great numbers of histone-reader pairs. Detailed structural analysis revealed delicate intermolecular network that governs the histone recognition by reader domains. The mechanistic study about reader-histone interaction could serve as a springboard for future therapeutic interventions when histone interaction by reader domain is misregulated during disease processes. A missing link in the field is about the combinatorial nature of histone modification patterns. With each individual PTM subject to dynamic regulations, neighboring PTMs are often controlled in concert, giving rise to unique combinatorial PTM patterns. The dynamics of histone PTM landscapes and their recognition mechanism by chromatin-reading modules remain largely uncharacterized in the complete context of native chromatin. The work presented in the following chapters addresses some of these challenges about combinatorial histone modifications and reader domains. Chapter 1 introduces the basic concepts and current views of combinatorial histone modification and reader domains. Chapter 2 highlights the development of a comprehensive histone peptide microarray that encompasses combinations of different histone PTMs. Use of the peptide microarray revealed context-specific recognition by reader domains. Such specific recognitions were employed to develop a chromatin reader-based affinity enrichment platform to reveal interconnections between nucleosomal histone PTMs. In Chapter 3, I further utilized peptide microarray and determined histone-binding preferences among closely related KDM4 (lysine demethylase 4) reader domains. In particular, I followed up on H3K23me3, a poorly understood histone modification. Structural and biochemical analysis of reader-histone interaction discovered molecular determinants for recognizing H3K23me3. Further analysis supports a novel epigenetic mechanism whereby H3K23me3-binding by KDM4B directs localized H3K36 demethylation during meiosis and spermatogenesis. Chapter 4 presents conclusions from this work and provides an outlook for the future research. The size constraints of the nucleus necessitate condensation of eukaryotic DNA into chromatin. The fundamental subunit of chromatin is the nucleosome, ĩ47 bp of DNA wound about the histone octamer. Each octamer typically contains two copies each of the canonical histones H2A, H2B, H3 and H4. However, packaging DNA limits its availability to enzymes necessary for the maintenance and expression of our heritable material. More precisely, all chromatin-dependent processes--transcription, replication, recombination, and repair--are affected by the position and occupancy of nucleosomes. Given the transcriptional challenges inherent to DNA packaging, this dissertation documents studies aimed at addressing this fundamental question: How does a cell modify chromatin to achieve proper gene expression? To this end, I pursued functional studies in S. cerevisiae of a potential chromatin modifier, Yta7, and a novel chromatin modification, H2A.Z acetylation. My studies on Yta7, a conserved bromodomain-containing protein with AAA-ATPase homology, identified this protein as a novel regulator of histone H3 eviction or degradation. Cells lacking Yta7 exhibited both increased levels of chromatin-incorporated histone H3 and decreased nucleosome spacing. Importantly, this modulation of H3 levels occurred post-transcriptionally. The yta7 Delta mutant's transcriptional defects were partially suppressed by decreased dosage of histones H3 and H4, indicating the transcriptional impact of this increased nucleosome density. Additionally, Yta7

associated with inducible genes only upon transcriptional activation, with prominent enrichment within open reading frames. Yta7 and its ATPase function were required for the proper induction of these genes. Further, loss of local Yta7 activity resulted in a 5' to 3' gradient of H3 accumulation within a large open reading frame upon transcriptional activation, indicating a direct requirement for Yta7's regulation of H3 levels at that gene. In support of a direct mechanism of histone eviction or degradation by Yta7, Yta7 directly interacts with histone H3 in vitro. Further, over-expressing Yta7 resulted in a 65% decrease in levels of chromatin-bound H3, as assayed by chromatin immunoprecipitation. Taken together, my studies support a model in which Yta7 utilizes the energy released upon ATP hydrolysis to evict and/or facilitate the degradation of histone H3. As bulk chromatin from cells without Yta7 exhibited increased nucleosome density and decreased dosage of either H3 or H4 suppresses the growth defect of the yta Delta mutant, Yta7 presumably evicts or degrades an H3/H4 dimer or tetramer. Thus, these studies identified a protein that limited the extent of DNA packaging, thereby facilitating RNA polymerase activity upon transcription. Restricting nucleosome density represents one mechanism for enabling transcriptional activation. Another possible mechanism is modifying the nucleosomes themselves, by covalently modifying the incorporated histones or changing which histones are incorporated. Although nucleosomes typically contain two copies of each canonical histone, histone variants, such as H2A.Z and H3.3, can be substituted at specific genomic locations for their cognate canonical histone. The histone H2A variant H2A.Z is conserved and essential in all multicellular eukaryotes assayed. Yeast cells lacking H2A.Z exhibit a broad range of chromatin-based phenotypes, including defective gene induction, genomic instability, and spreading of the Sir-silencing complex from heterochromatin into euchromatic domains. However, the importance of its N-terminal tail acetylations to these functions remained unclear. Therefore, I undertook studies to determine the genome-wide requirements for H2A.Z acetylation, assess the role of individual acetylation sites and identify which proteins might interpret these modifications. My work on H2A.Z acetylation indicated that the transcriptome of cells lacking H2A.Z acetylation exhibited fewer expression defects than cells lacking H2A.Z. In contrast to proposed roles in transcriptional activation, cells lacking H2A.Z acetylation exhibited a bias toward up-regulation of genes. Genes that were down-regulated in these cells, however, were highly enriched for telomere-adjacent genes, consistent with Sir silencing antagonism or altered telomeric structure. In keeping with more recent work, my data supported a model of acetylation-site equivalence and additive activity of H2A.Z acetylation. Additionally, this work identified the double bromodomain-containing TFIID-associated Bdf1 as interacting with H2A.Z in an acetylation-dependent manner in vivo. As Bdf1 is required to inhibit Sir-complex spreading from the telomeres, this work provides insight into the potential mechanism of Bdf1's Sir complex antagonism. Further work will have to be performed to determine if the down-regulation of telomere-adjacent genes in cells that cannot acetylate H2A.Z is Sir-dependent and whether these genes' requirement for acetylated H2A.Z is a direct one. However, these studies on H2A.Z acetylation are consistent with a model in which H2A.Z acetylation prevents chromatin condensation by the Sir proteins, an alternative mechanism for maintaining proper gene expression. Gene expression is strongly influenced by local chromatin state, begging the question of what role population genetic factors play in driving variability in chromatin state. Using a combination of traditional D. melanogaster crosses, fully sequenced genomes, and computational methods, we survey global autosomal variation that impacts position effect variegation (PEV), a traditional proxy for chromatin state. We find little evidence for involvement of segregating functional (non-synonymous) variants within>100 known autosomal modifiers of PEV. Instead, we find enrichment of small-effect variants located within regions of open chromatin, sites of origin recognition complex (ORC) binding, and highly occupied target (HOT) regions for transcription factors. These variants fail to fully explain observed phenotypic variance in PEV, with the remainder accounted for by variants with ever

smaller effect sizes. Further, we note only a small proportion of variants are explained through geneenvironment interaction, and we find no evidence for transgenerational transmission of chromatin state. Next we constructed a set of Y-chromosome replacement lines to probe the means by which altered heterochromatin content can impact chromatin states elsewhere in the genome. We reveal surprisingly high levels of heterogeneity among Y chromosomes from inferred counts of repetitive kmers and transposable elements. These variants show signs of functional constraint along with association to PEV and exceptionally strong associations to transcript counts from RNA-seq. Rapid evolution of Y-linked kmers and their impact on global gene expression is apparent from the degree of inter-population heterogeneity, including population-specific repeats. In summary, we identify involvement of a historically overlooked source of variation with functional consequences to gene expression. This work has immediate impact to informing current medical GWAS practice, and has further implications for refining evolutionary models of gene regulation. Plant somatic cells exhibit extraordinary developmental plasticity, yet they are able to stably maintain terminal identities. Although this capacity was recognized long ago, our mechanistic understanding of the establishment, maintenance, and erasure of cellular identities in plants remains limited. Manipulations of chromatin modifiers, particularly polycomb repressive complex 2 (PRC2), indicate chromatin-level regulation of cell identity is critical for establishing stable cell fates in plants. This is partially due to the fact that genes regulating embryo development and meristem identity are targets of PRC2-based repression in. Evidence also suggests developmental plasticity via reprogramming depends in part on plant differentiated cells' ability to re-establish stemness by accessing meristematic and embryonic gene expression programs. This happens naturally in some contexts; Kalanchoe daigremontiana clonally propagates by upregulating the expression of meristematic genes in leaf margins to reprogram differentiated cells to produce new seedlings. Reprogramming can also be induced experimentally; excision of the root stem cell niche in Arabidopsis causes differentiated root cells to revert to an embryo-like transcriptome to produce a new stem cell niche. Despite a growing body of literature describing reprogramming events and PRC2 in Arabidopsis thaliana, several questions remain. Namely, how do somatic cells supersede repressive chromatin states to reinstate developmental plasticity? If cells can so readily access these meristematic and embryonic transcriptional programs, how do plant cells specifically regulate when reprogramming can occur? In this dissertation, I use the Arabidopsis stomatal lineage to explore these phenomena in single cell types, thereby profiling cellular reprogramming with uniquely fine developmental and temporal resolution in plants. Stomata are structures on the surfaces of most land plants required for gas exchange between plants and their environment. Stomatal guard cells are the end product of a specialized lineage whose cell divisions and fate transitions ensure both production and pattern of cells in aerial epidermal tissues. These cell divisions and fate transitions are regulated by the sequential expression of a series of bHLH transcription factors that serve as master regulators of this developmental series: SPEECHLESS (SPCH), MUTE, and FAMA. The stomatal lineage is dynamic and flexible, altering stomatal production in response to environmental change. As such, the stomatal lineage is an excellent system to study how flexible developmental transitions are regulated in plants. In Chapter 1 I summarize the current knowledge of extrinsic and intrinsic regulation of stomatal development regulation. I also summarize current knowledge regarding chromatin-level regulation of cell fate stabilization in Arabidopsis and explain how the stomatal lineage can be a valuable model system for studying this phenomenon in plants. Guard cells can be manipulated such that they reprogram to the stomatal lineage initiation phase. In Chapter 2 I leverage a this to develop a cell-type specific reprogramming system than can be probed at the genome-wide scale for alterations in gene expression and histone modifications before and during reprogramming. I show that relationships among histone modification enrichments and gene expression in single cell types mirror trends from complex

tissue, and that dynamic regulation by PRC2 is critical for maintenance of guard cell identity. Surprisingly, I found guard cells may sense and resist inappropriate reprogramming, in part through PRC2-mediated repression of a regulator of wound-induced callus formation. I propose a model where negative regulation of pro-reprogramming genes in the absence of a wounding signal is partially responsible cell fate maintenance in Arabidopsis. Furthering the utility of the reprogramming datasets I generated in chapter 2 requires cognate datasets of the stomatal lineage initiation phase. However, cells in this phase of stomatal development are not accessible to isolation with currently available tools. In Chapter 3, I describe the optimization of tools to render these cells accessible. To that end, I sought to optimize the Isolation of Nuclei Tagged in specific Cell Types (INTACT) system for the stomatal lineage to facilitate collection of rare stomatal lineage progenitor cells. In parallel, I applied the novel technique, Cleavage Under Targets and Release Using Nuclease (CUT& RUN) to Arabidopsis samples, enabling genome-wide chromatin mapping using small numbers of cells, which dramatically improves the signal to noise ratio of traditional protein-DNA interaction profiling. This chapter details the development of these tools and datasets, are promising for application to the stomatal lineage. In Chapter 4 I address further questions to be considered regarding cellular reprogramming in plants. I also comment on the outlook for INTACT and CUT& RUN Arabidopsis stomatal lineage and propose future applications for them. Epigenetics studies heritable genetic changes that occur due to a change in gene function, generated through processes like DNA methylation, histone modification, etc. Epigenetic changes alter the microstructure of DNA or the associated chromatin proteins leading to gene activation or silencing. Chromatin is a macromolecular complex, consisting of DNA, RNA and protein found in cells. Its primary functions are packaging DNA into more compact and denser shape, preventing DNA damage, controlling gene expression and DNA replication. The structure of chromatin is subject to change depending on the stage of the cell cycle. The aim of this book is to present researches that have transformed the understanding of epigenetics and chromatin. It is a compilation of chapters that discuss the most vital concepts and emerging trends in these fields. It will be a valuable source of reference for students and researchers alike. Contemporary views on the structure and function of chromatin are presented and the history of the development of these ideas as well as the nature of the nucleic acid and protein components of chromatin are reviewed. The structure of chromatin is studied at several levels, and its modes of transcription and replication are analyzed. Chromatin provides researchers with a critical evaluation of current knowledge. It combines much information that has never before been assembled, and evaluates and interrelates it in a critical way. This has not been done before so that readers are not only provided with an overview, but with extensive references to the literature (there are about 2000 references in all). The centromere is a chromosomal region that enables the accurate segregation of chromosomes during mitosis and meiosis. It holds sister chromatids together, and through its centromere DNA–protein complex known as the kinetochore binds spindle microtubules to bring about accurate chromosome movements. Despite this conserved function, centromeres exhibit dramatic difference in structure, size, and complexity. Extensive studies on centromeric DNA revealed its rapid evolution resulting often in significant difference even among closely related species. Such a plasticity of centromeric DNA could be explained by epigenetic c- trol of centromere function, which does not depend absolutely on primary DNA sequence. According to epigenetic centromere concept, which is thoroughly d- cussed by Tanya Panchenko and Ben Black in Chap. 1 of this book, centromere activation or inactivation might be caused by modifications of chromatin. Such acquired chromatin epigenetic modifications are then inherited from one cell di- sion to the next. Concerning centromere-specific chromatin modification, it is now evident that all centromeres contain a centromere specific histone H3 variant, CenH3, which replaces histone H3 in centromeric nucleosomes and provides a structural basis that epigenetically defines centromere and differentiates it from the

surrounding chromatin. Recent insights into the CenH3 presented in this chapter add important mechanistic understanding of how centromere identity is initially established and subsequently maintained in every cell cycle. An early view of eukaryotic chromosomes was that of static structures, which stored DNA not in use within a given cell type. It was thought that packaging of DNA into higher levels of chromatin structure would suffice to repress gene expression and that the challenge to the cell would be to rescue specific sequences from these structures. The exten sive packaging of inactive DNA was considered the primary difference between eukaryotic and prokaryotic genomes and except for that point both would be similarly regulated by cis-acting sequences and trans acting factors. Our view of eukaryotic chromosomes has evolved dra matically over the last decade. The picture of chromosomes that is emerging is that of dynamic breathing organelles actively regulating the flow of genetic information from the genome. Indeed chromatin is so fluid that even maintaining gene quiescence is an active process and is tightly regulated. Chromatin dynamics is a consequence of protein complexes that modify histones, remove histone modifications, mobi lize nucleosomes or stabilize nucleosomes. Awide variety of such com plexes have now been described. Some are abundant and may play glo bal roles in chromosome fluidity and function. Others are more rare and specialized for specific functions at discreet loci. Moreover, several complexes share biochemical activities and genetic studies suggest overlapping functions in vivo. Many components of these complexes were first revealed in genetic screens, while others were discovered by novel cell biological or biochemical approaches. Marchantia polymorpha has become a model system to study land plant evolution because it is one of the earliest diverging land plants, possesses limited genetic redundancy and tools for functional genomics have become readily available. All land plants evolved from an algal ancestor with a haplobiontic life cycle with zygotic meiosis, meaning a multicellular gametophytic (n) body with the only diploid (2n) phase being the fertilized egg (zygote) that undergoes meiosis to release haploid spores. In contrast, land plants, or embryophytes, exhibit an alternation of generations - the gametophyte produces male and female gametes and upon fertilization the zygote undergoes mitotic divisions to form the sporophyte or embryo. Recent studies suggest that chromatin modification factors, including the Polycomb Repressive Complex 2 (PRC2), play a major role in phase transitions by repressing sporophyte specific genes, for example KNOX genes. KNOX and BELL proteins belong to the TALE class homeodomain superclass of proteins that are present in animals, plants and fungi. KNOX-BELL TALE proteins have been proposed to play a key role in the evolution of alternation of generations. In green algae, two different mating types of gametes fuse to produce the zygote, each containing either a KNOX- or a BELL-like protein. Both proteins are cytosolic until fertilisation, when the two proteins heterodimerise and translocate to the nucleus where they activate zygote gene expression and development. In land plants, a duplication event resulted in two distinct classes of KNOX genes, KNOX1 and KNOX2. The Marchantia genome encodes two KNOX1, one KNOX2 and two BELL genes. In this study I demonstrate that inducible disruption of Marchantia PRC2 function by expressing an artificial microRNA targeting MpE(z) in the gametophytic stage of the life cycle causes de-repression of sporophyte specific MpKNOX2 and MpBELLB genes that result in developmental arrest. Plants co-expressing either MpBELLA or MpBELLB and MpKNOX2 genes phenocopy this lethal phenotype of knock-down MpE(z) lines. While transcriptome data suggests antheridia specific expression of MpBELLA, MpKNX2 is expressed in the egg cell and sporophyte. In theory, these proteins come into physical contact upon fertilization. Protein-protein interactions of MpBELL and MpKNOX proteins with subsequent intracellular trans-localisation to the nucleus was validated. To elucidate additional target genes of MpE(z) and KNOX/BELL heterodimers, RNAseq on inducible knock-down MpE(z) lines and co-expression of either MpBELL gene with MpKNOX2 showed de-repression of various sporophyte specific genes, making them good candidates for further studies. Thus, I have revealed that the Marchantia PRC2 is necessary for sporophyte specific MpKNOX and MpBELL

repression. The interaction of both proteins could be demonstrated, and their expression in the gametophyte causes developmental arrest perhaps via activation/repression of downstream targets that probably reflect the determinate nature of the M. polymorpha sporophyte. The current model for DNA damage checkpoint initiation suggests that ssDNA, formed by 5' to 3' resection of DNA double strand breaks (DSBs), generates a signal that recruits and activates checkpoint signaling proteins. However, ssDNA formation is suppressed in the G1 checkpoint. In addition, this model does not explain why it is necessary for checkpoint proteins to bind adjacently to modified chromatin ten kilobases away from DSBs. Indeed, data published within the past decade have revealed a crucial role for chromatin modification in the DNA damage checkpoint response. Recent data show that chromatin modifications are necessary for recruitment and activation of yeast Rad9 and Crb2 as well as metazoan checkpoint adaptor proteins MDC1 and 53BP1. This thesis examines the role of chromatin modifications and DNA resection in immediate DNA damage checkpoint signaling. First, I determined that Rad9 chromatin association is necessary but not sufficient for checkpoint signaling and arrest in the telomere uncapping response. Next, I demonstrated that checkpoint signaling takes place in mutants deficient in long-range DNA resection or in mutants that fail to recruit checkpoint signaling proteins to ssDNA/RPA complexes. These studies contribute to the field by characterizing the contribution of Rad9 chromatin association and DNA resection to checkpoint signaling. I hope that in determining the mechanism of action for these events, they will contribute to the development of therapeutics used to sensitize tumors to radiation therapy. The ability to establish and transmit molecular memory of transcription is critical for cell fate identity and development, and often goes awry in disease. From a single totipotent embryo, development shapes phenotypically distinct cellular lineages from a single common genome. This trajectory of diversification was first investigated by Aristotle, which he referred to as 'epigenesis, ' and later was mapped to modern biology and what we know as epigenetics by Waddington. In recent decades, the term epigenetics has been further refined in the light of growing molecular insights; it now commonly refers to the activities of transcription factors, non-coding RNAs, and the modification of chromatin to establish heritable transcriptional activity states. Of the known mechanisms for the establishment of epigenetic states, covalent modification of the unstructured tail region of histone proteins has proven to be a pervasive and flexible one. Methylation, ubiquitylation, and acetylation--among numerous others--all act in concert as part of what has been referred to as a 'histone code.' Dependent of the constellation of modifications on resident histones, the transcriptional machinery that recognizes them confers either repressive or activating activities to the local chromatin environment. Critical for transcription, this histone code is yet more potent, as it has the capacity to be transmitted across the complete reorganization of chromatin that occurs through cell division. The principle mechanism of this activity is the ability of chromatin modifying machinery to execute a 'read-write' mechanism. When the chromosome duplicates, parental modified histones are randomly dispersed between daughter strands. Parental marks are then read by a suite of factors, and writing enzymes are recruited to copy marks to the local newly synthesized histones. Although this mechanism has been observed across nearly all eukaryotes, importantly, it is restricted to exclusively repressive, histone-methylation-driven states. Whether other states, for example active transcription driven by hyperacetylated histones can be epigenetically inherited has remained unknown. Aside from chromatin, many epigenetic traits are instead linked to the activity of heritable alternative conformational states of proteins alone. Such proteins are by and large prions, which are proteins that can assume multiple stable conformations, at least one of which can self-template to drive an intrinsically bi-stable switch. Long engendering a tight association with devastating neurodegenerative disease, we now know that prions can instead give rise to an unappreciated form of epigenetics. Biologically functional prions and prion-like proteins have now been identified in bacteria, fungi, and metazoans

where they regulate processes as diverse as translation, metabolism, and even long-term memory. Despite the conservation of this biology across life, it has been assumed that prions are rare within proteomes. By contrast, recent work has found that they are common, particularly among chromatin-templated processes (e.g. transcription factors, chromatin remodelers), suggesting a possible connection between prion conformational conversion and other epigenetic mechanisms. Here I have investigated one such prion that, through a regulated switching event, precipitates the establishment of an active, hyperacetylation-driven epigenetic state heritable through both mitotic and meiotic division. This prion, which we term [ESI+] for expressed sub-telomeric information, arose from the Snt1 scaffold protein. I identify a potential mechanism for its regulation through phosphorylation upon cell cycle arrest, and find that once activated the prion modifies the activity of Snt1 and its interactors in the Set3C complex, converting the complex from a repressor to an activator via recruitment of RNA pol II. This activity is most pronounced at sub-telomeres, where Snt1 and Set3C interfere with the conserved transcription regulator Rap1 binding. As a consequence of sub-telomeric activation, [ESI+] cells acquire broad tolerances to environmental stress, including antifungal drugs. Together, these results establish that prion conformational conversion can interface with chromatin, allowing for the inheritance of epigenetic states not previously considered heritable. While alone a striking example of how two forms of epigenetics can synergize to drive inheritance of active transcription, it by no means stands alone. Indeed, numerous chromatin-related proteins have prion-like properties, suggesting that this mechanism might be generally employed to regulate chromatin activity independently of other mechanisms. Further, even [ESI+] is likely not isolated to the laboratory, as dozens of wild strains of yeast exhibit elevated sub-telomeric expression evocative of the prion. While the limits of this biology remain to be explored, the example I present here strongly argues that it is far broader and more tightly integrated with other molecular systems than previously appreciated. Explores the Newly Discovered Link Between Nutrition and Epigenetics Current research suggests that nutrients are more than just food components and that certain nutrients can impact the expression of genes that lead to the development of chronic diseases. With contributions from experts in both fields, Nutrients and Epigenetics examines the epigenetic phenomena and the fascinating implications of diet on this largely uncharted field. Generously laden with tables and illustrations, many in color, this book addresses how nutrients alter physiologic and pathologic processes in the human body through epigenetic changes without affecting the DNA sequence. It also explains the detailed molecular structures of epigenetic phenomena and closely examines the current knowledge surrounding the biology of aging and embryonic growth regulation. Assesses the Likelihood of Clinical Applicability In one single compendium, this resource delineates the nutritional factors that further much-studied aberrant epigenetic patterns, such as DNA methylation, histone modifications, and chromatin remodeling. The book spotlights the influence of nutrition on epigenetic gene regulation, opening the way for counteracting future disease processes associated with epigenetic phenomena--a step that could potentially change the face of disease prevention and development. Epigenetic Gene Expression and Regulation reviews current knowledge on the heritable molecular mechanisms that regulate gene expression, contribute to disease susceptibility, and point to potential treatment in future therapies. The book shows how these heritable mechanisms allow individual cells to establish stable and unique patterns of gene expression that can be passed through cell divisions without DNA mutations, thereby establishing how different heritable patterns of gene regulation control cell differentiation and organogenesis, resulting in a distinct human organism with a variety of differing cellular functions and tissues. The work begins with basic biology, encompasses methods, cellular and tissue organization, topical issues in epigenetic evolution and environmental epigenesis, and lastly clinical disease discovery and treatment. Each highly illustrated chapter is organized to briefly summarize current research, provide appropriate pedagogical guidance,

pertinent methods, relevant model organisms, and clinical examples. Reviews current knowledge on the heritable molecular mechanisms that regulate gene expression, contribute to disease susceptibility, and point to potential treatment in future therapies Helps readers understand how epigenetic marks are targeted, and to what extent transgenerational epigenetic changes are instilled and possibly passed onto offspring Chapters are replete with clinical examples to empower the basic biology with translational significance Offers more than 100 illustrations to distill key concepts and decipher complex science This open access textbook leads the reader from basic concepts of chromatin structure and function and RNA mechanisms to the understanding of epigenetics, imprinting, regeneration and reprogramming. The textbook treats epigenetic phenomena in animals, as well as plants. Written by four internationally known experts and senior lecturers in this field, it provides a valuable tool for Master- and PhD- students who need to comprehend the principles of epigenetics, or wish to gain a deeper knowledge in this field. After reading this book, the student will: Have an understanding of the basic toolbox of epigenetic regulation Know how genetic and epigenetic information layers are interconnected Be able to explain complex epigenetic phenomena by understanding the structures and principles of the underlying molecular mechanisms Understand how misregulated epigenetic mechanisms can lead to disease An early view of eukaryotic chromosomes was that of static structures, which stored DNA not in use within a given cell type. It was thought that packaging of DNA into higher levels of chromatin structure would suffice to repress gene expression and that the challenge to the cell would be to rescue specific sequences from these structures. The exten sive packaging of inactive DNA was considered the primary difference between eukaryotic and prokaryotic genomes and except for that point both would be similarly regulated by cis-acting sequences and trans acting factors. Our view of eukaryotic chromosomes has evolved dra matically over the last decade. The picture of chromosomes that is emerging is that of dynamic breathing organelles actively regulating the flow of genetic information from the genome. Indeed chromatin is so fluid that even maintaining gene quiescence is an active process and is tightly regulated. Chromatin dynamics is a consequence of protein complexes that modify histones, remove histone modifications, mobi lize nucleosomes or stabilize nucleosomes. Awide variety of such com plexes have now been described. Some are abundant and may play glo bal roles in chromosome fluidity and function. Others are more rare and specialized for specific functions at discreet loci. Moreover, several complexes share biochemical activities and genetic studies suggest overlapping functions in vivo. Many components of these complexes were first revealed in genetic screens, while others were discovered by novel cell biological or biochemical approaches. Current Topics in Developmental Biology Genomics has gathered broad public attention since Lamarck put forward his top-down hypothesis of 'motivated change' in 1809 in his famous book "Philosophie Zoologique" and even more so since Darwin published his famous bottom-up theory of natural selection in "The Origin of Species" in 1859. The public awareness culminated in the much anticipated race to decipher the sequence of the human genome in 2002. Over all those years, it has become apparent that genomic DNA is compacted into chromatin with a dedicated 3D higher-order organization and dynamics, and that on each structural level epigenetic modifications exist. The book "Chromatin and Epigenetics" addresses current issues in the fields of epigenetics and chromatin ranging from more theoretical overviews in the first four chapters to much more detailed methodologies and insights into diagnostics and treatments in the following chapters. The chapters illustrate in their depth and breadth that genetic information is stored on all structural and dynamical levels within the nucleus with corresponding modifications of functional relevance. Thus, only an integrative systems approach allows to understand, treat, and manipulate the holistic interplay of genotype and phenotype creating functional genomes. The book chapters therefore contribute to this general perspective, not only opening opportunities for a true universal view on genetic information but also being key for a general understanding of

genomes, their function, as well as life and evolution in general. This book highlights the latest breakthrough developments in bioinformatics. It presents a series of timely, in-depth reviews, drug clinical trial studies, biodiversity informatics and thematic issues. In addition, it includes insightful reviews on advances in computational molecular/structural biology, which address areas such as computing in biomedicine and genomics, computational proteomics and systems biology, and metabolic pathway engineering. Innovations in these fields have direct impacts on key issues related to healthcare, medicine, genetic disorders, the development of agricultural products, renewable energy, and environmental protection. Written by respected leaders in the field and covering a wide range of topics involving the integration of biology with computer and information science, the book offers an ideal basis for teaching at the undergraduate and graduate levels. It can also be used for self-instruction by research investigators interested in applying bioinformatics-based analytical methods and information technologists working with academic and industrial laboratories.