In this issue of Epigenetics

Barbara P Rattner
Landes Bioscience; San Diego, CA USA

Kinases and Chromatin Structure
pp. 1008–12

Chromatin remodeling factors control chromatin structure and are in turn regulated by a number of chemical and developmental signals in response to changes in the cellular environment. Miotto discusses recent findings by the laboratories of Sharon Dent and Steve Jackson that suggest that, in different contexts, changes in chromatin structure may signal back to intracellular signaling pathways to regulate cell fate, challenging the traditional view of epigenetics.

The Human Bladder Cancer DNA Methylome
pp. 1013–22

The identification of improved strategies for early detection, treatment and monitoring of the progression of bladder cancer is a high priority in cancer research. Aberrant DNA methylation in single or multiple cancer-related genes has been found in human bladder tumors, cancer cell lines and urine sediments, and correlated with many clinicopathological features of this disease, including tumor relapse, muscle-invasiveness, and survival. A timely review by Besaratinia et al. summarizes recent research on aberrant DNA methylation in connection with human bladder cancer. The identification of potentially reversible aberrant DNA methylation events that initiate and promote bladder cancer development may highlight biological markers for early diagnosis, effective therapy, and accurate prognosis of this malignancy.

miRNAs in Speech and Language Disorders
pp. 1023–9

Speech disorders, which affect sound generation, and language disorders, such as dyslexia and specific language impairment, are difficult to diagnose, especially when a patient presents more than one disorder at the same time. A review by Rudov et al. combines data from the literature with an in silico approach and attempts to identify putative miRNAs that may have a key role in these diseases. The authors suggest that the use of new miRNAs could have an important impact on the understanding and diagnosis of these three diseases.

DNA Methylation in Parkinson Disease
pp. 1030–8

Parkinson disease, a multifactorial neurodegenerative disorder in which both genetic and environmental factors play important roles, has recently been associated with epigenetic mechanisms. The identification of early pathological changes is crucial to enable therapeutic interventions before major neuropathological damage occurs. Masliah et al. investigated genome-wide DNA methylation in brain and blood samples from Parkinson disease patients and observed a distinctive pattern of methylation involving many genes previously associated to the disease, supporting a role for epigenetic alterations as a molecular mechanism in neurodegeneration. Moreover, the authors suggest that blood might hold promise as a surrogate for brain tissue to detect DNA methylation in patients and as a source for biomarker discovery.

Quantifying Allele-Specific Expression
pp. 1039–42

Yang et al. have developed a rapid and sensitive quantitative assay for the measurement of individual allelic ratios. The authors argue that the assay minimizes time and labor, does not need special restriction endonuclease enzymes for polymorphic sites, and avoids heteroduplex formation seen with traditional quantitative PCR-based methods. The method, termed pyrosequencing for imprinted expression (PIE), shows improved sensitivity and is capable of distinguishing 1% differences in allelic expression.

Cutaneous Melanoma and Epigenetic Regulation of REG1A
pp. 1043–52

In this issue, Sato et al. studied the regulation of REG1A, a gene that plays an important role in tissue regeneration and cell proliferation in melanoma. The authors studied whether REG1A is expressed in cutaneous melanoma and if its expression status can predict prognosis in cutaneous melanoma patients with metastasis. They showed that promoter CpG methylation regulates REG1A expression in melanoma cells and that REG1A expression status may be useful as a biomarker in melanoma patients for sensitivity to chemotherapeutic agents.
Beckwith-Wiedemann syndrome (BWS) is a rare disorder characterized by overgrowth and predisposition to embryonal tumors. The disease is caused by various epigenetic and/or genetic alterations that dysregulate the imprinted genes on chromosome region 11p15.5. It is crucial to identify molecular biomarkers that could reinforce the clinical diagnosis of BWS and recognize BWS patients with cancer susceptibility. Calvello et al. present a pyrosequencing molecular assay that involves the quantitative evaluation of the methylation profiles of ICR1 and ICR2. This approach was used to explore epigenotype-phenotype correlations in patients diagnosed using the current criteria for BWS and in patients with suspected BWS. Evaluation of ICR1 and ICR2 methylation by pyrosequencing in BWS can improve epigenotype-phenotype correlations, detection of methylation alterations in suspected cases, and identification of uniparental disomy.

PCBs: Epigenetic Effects Mediated by Jarid1b
pp. 1061–8

Exposure to environmental endocrine disrupting compounds, such as polychlorinated biphenyls (PCBs), widely diffused in the environment may produce epigenetic changes that affect the endocrine system. PCBs activate AR transcriptional activity and this effect is potentiated by the demethylase Jarid1b, which catalyzes the removal of H3K4me3. Casati et al. now investigated the effect of PCBs and dihydrotestosterone (DHT) on the functional interaction between AR and Jarid1b using HEK293 cultured cells. They found that the effect of PCBs, but not of DHT, needs the presence of Jarid1b and of at least two DNA binding sites for Jarid1b.

Gestational/Maternal Factors and Methylation at the IGF2/H19 Locus
pp. 1069–79

The insulin-like growth factor 2 (IGF2)/H19 locus, which is crucial for prenatal growth, is susceptible to environmental factors affecting its epigenetic state. Maternal factors, including folate intake and smoking, play important roles in the regulation of DNA methylation at this locus. Loke et al. investigated the relationship between multiple shared and non-shared gestational/maternal factors and DNA methylation at four IGF2/H19 DMRs in newborn cell types from monozygotic and dizygotic twins. The results of this important study are summarized in this issue of Epigenetics.

Epigenetics of Toxicant-Induced Malignant Transformation
pp. 1080–8

Genome-wide epigenetic changes are characteristic of malignancy. In this issue, Severson et al. studied changes produced in the epigenome during toxicant-mediated malignant transformation with the goal of identifying underlying epigenetic drivers of environmental toxicant-induced carcinogenesis. Gene promoter DNA methylation and gene expression profiling of arsenite-transformed prostate epithelial cells present a negative correlation between gene expression changes and DNA methylation changes; however, less than 10% of the genes with increased promoter methylation were downregulated. The authors show that a majority of the DNA hypermethylation events occur at H3K27me3 marked genes that were already transcriptionally repressed and found that actively expressed C2H2 zinc finger genes marked with H3K9me3 on their 3’ ends were favored targets of DNA methylation-linked gene silencing. These studies associate toxicant exposure with widespread silencing of ZNF genes by DNA hypermethylation-linked H3K9me3 spreading, further implicating epigenetic dysfunction as a driver of toxicant associated carcinogenesis.

Analysis of MBD3 and DNA Demethylation by FCS
pp. 1089–100

Cui et al. record the dynamics of DNA demethylation using recombinant methyl-binding domain 3 (MBD3) protein fused to GFP in living cells under hypoxia and Decitabine treatment. The authors used fluorescence correlation spectroscopy (FCS) to monitor the diffusion dynamics of MBD3. They showed DNA replication-independent decrease of 5mC/5hmC under hypoxia and DNA replication-dependent decrease under Decitabine treatment. By monitoring the diffusion of bound and unbound MBD3 in the nucleus the authors were able to identify and characterize hypoxia-sensitive cells from insensitive/tolerant cells, as well as the respective contribution to active demethylation in a time-dependent manner. This is the first time that the dynamic process of DNA demethylation is correlated with the biophysical properties of the corresponding DNA binding proteins in live single cells by single molecule spectroscopy.

H3S10 O-Acetylation
pp. 1101–13

Britton et al. present their findings on a novel class of histone posttranslational modifications: serine, threonine and tyrosine O-acetylation. These unique marks have been found only on histone H3 and appear to be conserved in many species, ranging from yeast to human. H3S10ac is potentially linked to cell cycle progression and cellular pluripotency.

DNA Methylation and Aging
pp. 1114–22

Somatic stem cells are able to generate replacements for lost and damaged cells, but their regenerative capacity diminishes with age. Taiwo et al. studied the involvement of epigenetic changes in somatic stem cell aging, using murine hematopoiesis as a model system. Associated with age, the authors observed global loss of
DNA methylation and an increase in methylation at about 100 CpG islands, named aging-specific differentially methylated regions (aDMRs). They also report that DNA methylation patterns are well preserved during hematopoietic stem cell aging, confirm that PCRC2 targets are increasingly methylated with age, and suggest that *sdpr* expression changes in these cells may be regulated via age-based changes in DNA methylation.

**Meeting Report**  
**pp. 1123–4**

Lowe and Morris summarize the highlights of the 2nd Annual Infinium HumanMethylation450 Array Workshop, held at Queen Mary, University.