

# In this issue of *Epigenetics*

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## On the Transfer of SV40 Epigenetic Information pp. 528–34

In eukaryotes, epigenetic information can be encoded in parental cells through modification of histones and subsequently passed on to daughter cells in a process known as transgenerational epigenetic regulation. Simian Virus 40 (SV40) is a well-characterized virus whose small circular DNA genome is organized into chromatin and, as a consequence, undergoes many of the same biological processes observed in cellular chromatin. Milavetz et al. have analyzed SV40 chromatin from minichromosomes and virions for the presence of modified histones and demonstrated that SV40 chromatin is capable of passing biologically relevant transgenerational epigenetic information between infections.

## A DNA Methylation Signature for Pediatric Pre-B Cell ALL pp. 535–41

The mechanisms leading to pre-B cell acute lymphoblastic leukemia (ALL) are poorly understood. Wong et al. have now studied whether DNA methylation plays a role in ALL and have defined a genome-scale DNA methylation profile associated with the *ETV6-RUNX1* subtype of pediatric ALL. The authors show that recurrent aberrant genomic methylation is a common feature of pre-B ALL, suggesting a shared pathway for disease development. In addition, they reveal new DNA methylation markers associated with disease, identifying putative targets for the development of novel epigenetic-based therapies.

## Methylome of a DNMT3B Mutant Patient pp. 542–50

ICF (immunodeficiency, centromere instability and facial anomalies) syndrome is associated with mutations in the DNA methyltransferase DNMT3B, which results in a reduction of enzyme activity. Aberrant expression of immune system genes and hypomethylation of pericentromeric regions accompanied by chromosomal instability were determined as alterations driving the disease phenotype. Heyn et al. have now performed whole-genome DNA methylation studies and detected a genome-wide decrease on the methylation level, with the most profound changes occurring in inactive heterochromatic regions, satellite repeats and transposons. Interestingly, transcriptional active loci and rRNA repeats escaped global hypomethylation. Despite a genome-wide loss of DNA methylation, the epigenetic landscape and crucial regulatory structures were conserved. In addition, a functional association between promoter methylation and the ICF syndrome immunodeficient phenotype was detected in genes related to the B-cell receptor mediated maturation pathway.

## Epigenetic Control of *Wnt5a* during Colon Cancer Metastasis pp. 551–8

Aberrant expression of *Wnt5a*, one of the WNT signaling factors, has been reported during colon cancer development and progression. Li and Chen found that both mRNA and protein expression of *Wnt5a* were decreased in the highly metastatic human colon cancer cell line SW620 compared with the non-metastatic human colon cancer cell SW480. The authors tested the hypothesis that silencing of

*Wnt5a* in metastatic human colon cancer cells is related to altered epigenetic modifications and were able to show the involvement of histone modifications in the transcriptional regulation of *Wnt5a*. In addition, their results suggest that HDAC inhibitors play critical roles in the WNT signaling pathway and cell physiology that relate to metastasis.

## Key DNA Methylation Changes during Lung Cancer Development pp. 559–66

With the goal of identifying common changes in DNA methylation associated with the development of non-small cell lung cancer, Nelson et al. used paired tumor and non-tumor lung tissues from 146 individuals from three independent populations and identified the top gene-loci representing an increase in methylation (*HOXA9* and *SOX1*) and decrease in methylation (*DDIT1*). The magnitude and strength of these changes were consistent across squamous cell and adenocarcinoma tumors. These results suggest that the identified genes consistently have altered methylation in lung tumors and should be included in translational studies that aim to develop screenings for early disease detection.

## Novel Epigenetic Changes in CLL pp. 567–78

Pei et al. performed a comprehensive DNA methylation analysis of CD19<sup>+</sup> B-cells from chronic lymphocytic leukemia (CLL) patients and normal control samples. The authors determined the methylation status of 1.8–2.3 million CpGs in the CLL genome and found that about 45% of these CpGs were located in more than 23,000 CpG islands. While global CpG methylation was similar between CLL and normal B-cells, more than 1,700 gene

promoters were differentially methylated in at least one CLL sample when compared with normal B-cell samples. Among the genes aberrantly hypermethylated in CLL, they identified all HOX gene clusters and a significant number of WNT signaling pathway genes. Hypomethylation occurred more frequently in introns, exons and 3'-UTRs.

### **Epigenetic Modifications in the *DUX4* Promoter in FSHD pp. 579–84**

Balog et al. studied the relationships between epigenetic parameters correlating with a relaxed chromatin state of the *DUX4* promoter region and clinical severity of facioscapulohumeral muscular dystrophy (FSHD) patients. Their results confirm that D4Z4 chromatin relaxation is in fact associated with FSHD. The authors could also establish a possible relationship between clinical and epigenetic parameters in patient fibroblasts, but not in myoblasts. In addition, other results suggest that the vastus lateralis muscle could be used to study surrogate markers of overall disease severity.

### **HCMV and DNA Methylation pp. 585–93**

Human Cytomegalovirus (HCMV) is a ubiquitous herpesvirus that infects and establishes latency in the majority of the human population and may cause fatal infections in immunocompromised patients. Esteki-Zadeh et al. investigated the interactions between HCMV infection and DNA methylation in different host cells. The authors found that HCMV infection results in profound effects on the host cell DNA methylation machinery and is associated with inflammation in vivo. These results contribute to the further understanding of mechanisms involved in DNA methylation abnormalities in physiological and pathological conditions.

### **DNA Methylation from 0 to 2 pp. 594–605**

Prenatal development and early childhood are critical periods for establishing the

tissue-specific epigenome and may have a profound impact on health and disease in later life. Wang et al. examined the individual variation and longitudinal pattern of genome-wide DNA methylation levels from birth through the first two years of life in a defined group of children and observed a wide range of inter-individual variations in genome-wide methylation at each time point. Specifically, they identified CpG sites (located within genes with important functions in immunity and inflammation) with significant intra-individual longitudinal changes in the first two years of life throughout the genome.

### **On Diet, Lifestyle Risk and DNA Methylation pp. 606–14**

Altered levels of global DNA methylation and gene-specific methylation of promoter regions can impact cancer risk, but little is known about their environmental determinants. Zhang et al. examined the association between lifestyle factors and levels of global genomic methylation and *IL-6* promoter methylation in white blood cell DNA of cancer-free subjects. The authors found that the levels of *IL-6* promoter methylation were not significantly correlated with age, gender, race/ethnicity, body mass index, physical activity or diet, including overall dietary patterns and individual food groups and nutrients. LINE-1 methylation was found to be associated only with dietary folate intake.

### **Standardization and Quality Controls for MeDIP pp. 615–25**

MeDIP (Methylated DNA Immunoprecipitation) is a relatively recent technique aimed to enrich the methylated fraction of DNA with an antibody directed against 5-methyl-cytosine. MeDIP processed samples are suitable for investigation of the methylation status of specific genomic loci and for performing genome-wide screening when hybridized to DNA methylation microarrays or analyzed by deep sequencing. Lisanti et al. describe a useful and timely standardization protocol and quality controls to

assess the specificity, reproducibility and efficiency of the MeDIP procedure.

### **Developmental Regulation and Imprinting of *Tnfrsf* Genes pp. 626–34**

Tumor necrosis factor receptor superfamily is composed of at least 26 members in the mouse, three of which (*Tnfrsf 22, 23* and *26*) exist as a cluster within the imprinted *Kcnq1* domain on chromosome 7. de la Casa Esperón et al. found that these three genes are expressed during mouse embryonic development with a strong maternal bias, indicating that they may be affected by the KvDMR, the *Kcnq1* imprinting control region. Phylogenetic analyses suggest that TNFRSF sequences were duplicated and/or degenerated or eliminated from the *KCNQ1* region several times during the evolution of mammals.

### **DMSO Effect in Pre-osteoblastic Cells pp. 635–51**

Artificial induction of active DNA demethylation appears to be a possible and useful strategy in molecular biology research and therapy development. Dimethyl sulfoxide (DMSO) causes phenotypic changes in embryonic stem cells by altering the genome-wide DNA methylation profiles. Thaler et al. now report that DMSO increases global and gene-specific DNA hydroxymethylation levels in pre-osteoblastic cells. After one day, DMSO increased the expression of genes involved in DNA hydroxymethylation and nucleotide excision repair and decreased the expression of genes related to DNA methylation. The authors observed an increase of 5-hmC with a concomitant loss of methyl-cytosines on *Fas* and *Dlx5* promoters, as well as an increase in global 5-hmC and loss in global DNA methylation. This effect on promoter and global methylation was reduced/reversed after five days. Their results suggest that DMSO initially stimulates apoptosis via hydroxymethylation of the *Fas* promoter in a subpopulation of the heterogeneous MC3T3-E1 cell line, leaving a cell population of extra-cellular matrix producing osteoblasts.

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**Differential “Genome-wide” DNA Methylation in Placental and Somatic Tissues**  
pp. 652–63

DNA methylation of CpGs located in two types of repetitive elements—LINE-1 and Alu—is used to assess “global” changes in DNA methylation in studies of human disease and environmental exposure. Nevertheless, these repetitive elements contribute only to close to 30% of all base pairs in the human genome. Few studies have investigated whether repetitive element DNA methylation is associated

with DNA methylation at other genomic regions, or the biological and technical factors that influence potential associations. Price et al. now assessed LINE-1 and Alu DNA methylation and show that evolutionary age and assay method affect the assessment of repetitive element DNA methylation. The authors also demonstrate that each of these dispersed sequences exhibits different patterns of tissue-specific DNA methylation. Interestingly, correlation of DNA methylation suggests an association between LINE-1 and weak CpG island DNA methylation in some of the tissues examined.

**Book Review**  
pp. 664–6

We are excited to start a new section in which we will review books intimately related with the epigenetics field. In this issue, we took a look at the book *Non-coding RNAs and the Epigenetic Regulation of Gene Expression: Drivers of Natural Selection*, edited by Kevin Morris and published by Caister Academic Press in February 2012.

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