Epigenetics 8:6, 559–560; June 2013; © 2013 Landes Bioscience

In this issue of *Epigenetics*

Barbara P. Rattner

Landes Bioscience; San Diego, CA USA

Epigenetic and Myelodysplastic Syndromes pp. 561–70

Myelodysplastic syndromes (MDS) are clonal disorders of hematopoietic stem cells that show increased risk of leukemic transformation. Several studies have suggested a role for epigenetic mechanisms in MDS pathogenesis and prognosis; moreover, demethylating agents have already been used for the treatment of MDS. Vasilatou et al. review the current knowledge concerning the role of epigenetic alterations and, specifically, microRNAs in MDS pathogenesis and treatment.

C2ORF40: A Suppressor of Breast Cancer Cell Proliferation and Invasion pp. 571–83

has recently been suggested as a candidate tumor suppressor gene in breast cancer. Now, Lu et al. show that *C2ORF40* is frequently silenced in human primary breast cancers and cell lines via promoter hypermethylation. The authors demonstrate that *C2ORF40* mRNA level is significantly associated with patient disease-free survival and distant cancer metastasis and that its overexpression inhibits breast cancer cell proliferation, migration and invasion. These results suggest that *C2ORF40* acts as a tumor suppressor gene in breast cancer pathogenesis and progression and place it as a candidate prognostic marker for this disease.

Homocysteine, DNA Methylation and Schizophrenia pp. 584–90

Elevated total homocysteine in plasma has been suggested as a risk factor for schizophrenia (SCZ), as various biological effects of hyperhomocysteinemia have been proposed to be relevant to the pathophysiology of the disease. Because no studies have examined yet the relationship between homocysteine and genome-wide DNA methylation in SCZ, Kinoshita et al. have now analyzed the relationship between plasma total homocysteine and DNA methylation patterns in peripheral leukocytes of patients with SCZ. The authors observed significant homocysteine-related changes in DNA methylation at 1,338 CpG sites that were located across different gene regions, including promoters, gene bodies and 3′ untranslated regions.

A Bovine Model for Beckwith-Wiedemann Syndrome pp. 591–601

Beckwith-Wiedemann syndrome (BWS) is a human loss-of-imprinting syndrome primarily characterized by macrosomia, macroglossia and abdominal wall defects. BWS has been associated with misregulation of two clusters of imprinted genes. Children conceived with the use of assisted reproductive technologies (ART) appear to have an increased incidence of BWS. In ruminants, ART can also induce a similar overgrowth syndrome called LOS (large offspring syndrome). Chen et al. have now studied whether LOS shows similar loss-of-imprinting at loci known to be misregulated in BWS. Their results show phenotypic and epigenetic similarities between LOS and BWS and, therefore, the authors propose the use of bovine LOS as an animal model to investigate the etiology of BWS.

Offspring Epigenomic Consequences of Maternal Obesity and Diabetes pp. 602–11

It is now accepted that intrauterine nutrition can program offspring metabolism, creating stable changes in physiology that may have significant health consequences. Li et al. present the first study of offspring epigenomic consequences of exposure to maternal obesity and diabetes. Using a mouse model of natural-onset obesity that allows comparison of genetically identical mice whose mothers were either obese and diabetic or lean with a normal metabolism, the authors found that the offspring of obese mothers have a latent metabolic phenotype that is unmasked by exposure to a Western-style diet, resulting in glucose intolerance, insulin resistance and hepatic steatosis. The authors suggest that these phenotypes predispose offspring to respond poorly to suboptimal environments, which may be avoidable if postnatal nutrition is carefully controlled.

Dietary Isothiocyanates in Colon Cancer pp. 612–23

Cruciferous vegetables, such as broccoli, Brussels sprouts, cabbage and cauliflower, protect against colorectal cancer and other leading causes of cancer-related death. The beneficial effects of cruciferous vegetables have been attributed, at least in part, to their content of isothiocyanates (ITCs). Rajendran et al. used human colon cancer cells to show that dietary ITCs inhibit histone deacetylase (HDAC) activity and increase HDAC protein turnover with potency proportional to their alkyl chain length. Depending on the ITC and treatment conditions, phenotypic outcomes

Correspondence to: Barbara P. Rattner; Email: barbara@landesbioscience.com
Submitted: 05/13/13; Accepted: 05/13/13
http://dx.doi.org/10.4161/epi.25270

included cell growth arrest, autophagy and apoptosis. Importantly, colon cancer cells were more susceptible than non-cancer cells to ITC-induced DNA damage, an observation that could be used for improving current therapeutic strategies.

A Methylome Analysis of Ovarian Tumors pp. 624–34

Ovarian cancer progression is associated with the accumulation of epigenetic alterations and aberrant DNA methylation in gene promoters. Huang et al. have now globally examined DNA methylation in ovarian cancer using next-generation sequencing technology. The authors identified a total of 577 DMRs that distinguished malignant from non-malignant ovarian tissues. Of these, 63 DMRs correlated with poor progression-free survival. In a panel of ovarian cancer lines, Hedgehog pathway members *ZIC1* and *ZIC4* were found to be concordantly hypermethylated and silenced; *ZIC1* and *ZIC4* repression correlated with increased proliferation, migration and invasion.

GPR1AS: A Human Functional Homolog to Mouse Zdbf2linc pp. 635–45

Long non-coding RNAs (lncRNAs), which are transcribed from the intergenic regions of animal genomes, play important roles in key biological processes. In mice, Zdbf2linc was recently identified as a lncRNA isoform of the paternally expressed imprinted *Zdbf2* gene. It is thought that the functional role of Zdbf2linc may be to control parent-of-origin-specific expression of protein-coding neighbors through epigenetic modification in cis. Kobayashi et al. identified GPR1AS, a novel imprinted lncRNA, encoded in the human *GPR1-ZDBF2* intergenic region. Although *GPR1AS* contains no human *ZDBF2* exons, this lncRNA is transcribed in the antisense orientation from the *GPR1* intron to a secondary, differentially methylated region upstream of the *ZDBF2* gene, similar to mouse Zdbf2linc. In this work, the authors demonstrate that epigenetic regulation mechanisms in the imprinted *GPR1-GPR1AS-ZDBF2* region are well conserved between human and mouse genomes despite the poor sequence conservation of the intergenic lncRNAs. The authors suggest that lncRNAs with highly conserved epigenetic and transcriptional regulation across species (but without significant sequence conservation) may have arisen by divergent evolution from a common ancestor.

DNA Methylation Analysis of Primary Hyperparathyroidism pp. 646–55

Sulaiman et al. have now investigated epigenetic mechanisms involved in primary hyperparathyroidism by quantifying CpG island promoter methylation density of several candidate genes in parathyroid tumors and normal parathyroid references. In addition, the authors also assessed global methylation levels for LINE-1. Adenomas displayed frequent hypermethylation of *APC 1A*, *RASSF1A*, and β-catenin, whereas global methylation density was similar in tumors and parathyroid reference samples. In general, hypermethylated genes also showed reduced expression in parathyroid adenomas.

Zebularine and Brostallicin in Prostate Cancer Cells pp. 656–65

Prostate cancer cells usually present methylation of the *GSTP1* gene promoter and, therefore, low levels of GST-pi expression and activity. In these cells, brostallicin, a DNA minor groove binder, shows poor antitumor activity. Sabatino et al. have now tested whether pretreatment of heavily *GST*-methylated prostate cancer cells with demethylating agents could enhance the activity of brostallicin. The authors found that pretreatment with demethylating agents enhanced the in vitro activity of brostallicin in LNCaP cells. In particular, the use of zebularine in vivo induced an enhancement of brostallicin activity comparable to that obtained by transfecting the human *GSTP1* gene in LNCaP cells in vitro. These findings highlight the potential therapeutic value of combining demethylating agents and brostallicin in tumors with *GST*-methylation that poorly respond to brostallicin.

Epigenetic Switches in Tobacco Transgenes pp. 666–76

In plants, transcriptional gene silencing (TGS) and posttranscriptional gene silencing (PTGS) are typically associated with DNA methylation and often induced by siRNAs in a process called RNA-directed DNA methylation. Whereas in TGS methylation of the gene promoter inactivates transcription, in PTGS (which merely affects transcript stability and/or its translation rate), methylation occurs in cytosines within the transcribed region of the gene. Křížová et al. studied histone modification marks imposed on tobacco transgene loci during PTGS and TGS during dedifferentiation of cells in callus culture. The authors present a thorough analysis of the relationships between transgene expression, DNA methylation and histone modification.