Ing1: Linking DNA Demethylation and Histone Modifications pp. 679–84

Active DNA demethylation occurs both on a genome-wide level and on gene-specific scale. Whereas most genome-wide erasure of methylation marks during early development appears to be catalyzed by members of the ten-eleven translocation oxygenases, gene-specific demethylation seems to be mediated by short and long patch DNA excision repair enzymes. The Gadd45a protein regulates gene-specific demethylation within specific regulatory sequences of limited length, but the molecular mechanisms of its function are not understood. A timely Point-of-View article by Schomacher discusses the role of protein inhibitor of growth 1 (Ing1), a reader of the active chromatin mark H3K4me3, in the binding and guidance of Gadd45a to target sites, thus linking the histone code with DNA demethylation.

The MORC Family of Chromatin Remodelers pp. 685–93

Microrchidia (MORC) is a highly conserved nuclear protein superfamily with widespread domain architectures that intimately link these proteins with signaling-dependent chromatin remodeling and epigenetic regulation. Li et al. discuss recent advances in the understanding of these unique domain architectures and their potential contribution to epigenetic control of DNA template-dependent processes such as transcription and DNA damage response. Because deregulation of MORCs has been linked with human cancer and other diseases, the study of the structure and function of these proteins may lead to the development of new approaches to intersect with the functionality of this family of chromatin remodeling proteins to correct associated pathogenesis.

Epigenetic Biomarkers of Immune Function pp. 694–702

Epigenetic mechanisms such as DNA methylation and histone modifications regulate the expression of immune system-related genes, modifying the development of the innate and adaptive immune responses. Suárez-Álvarez et al. review recent discoveries concerning the epigenetic regulation of the immune system, and how this knowledge could be translated to the field of transplantation. Understanding these epigenetic mechanisms could help the design of new therapeutic strategies that could modulate the immune response after transplantation. For example, the detection of epigenetic marks in key immune genes could be useful as biomarkers of rejection and progression among transplanted patients.

HIV and Oral Cavity Infections pp. 703–9

HIV-infected subjects on highly active antiretroviral therapy (HAART) are susceptible to comorbid microbial infections in the oral cavity. Ghosh et al. observed that primary oral epithelial cells (POECs) isolated from HIV+ subjects on HAART grow more slowly and are less innate immune responsive to microbial challenge when compared with POECs from normal subjects. These aberrant cells also demonstrate epigenetic differences that include reduction in histone deacetylase 1 levels and reduced total DNA methyltransferase (DNMT) activity. The DNMT activity correlates well with global DNA methylation, indicating that aberrant DNMT activity in HIV+ (on HAART) POECs leads to an aberrantly methylated epithelial cell phenotype. These results support the hypothesis that, in HIV+ patients on HAART, epigenetic changes in key genes result in increased vulnerability to microbial infection in the oral cavity.

On the Epigenetic Plasticity of the Rat Hypothalamus pp. 710–9

High amount of vitamins, especially folate, are consumed during pregnancy causing later-life effects on the offspring. Cho et al. tested, using rat mothers on high multivitamin gestational diets, whether folate accounts for the observed increase in offspring metabolic syndrome. The male offspring of dams fed a high-folate (10-fold folate) diet during pregnancy and weaned to either the recommended vitamin (RV) or high-folate diets were compared with those born to RV dams and weaned to RV diet for 29 weeks. Food intake and body weight were highest in offspring of high-folate dams fed the RV diet. In contrast, the high-folate pup diet in offspring of high-folate dams reduced food intake, body weight and glucose response to a glucose load, and improved glucose response to an insulin load. Remarkably, high-folate alone in either gestational or pup diet modified gene expression of feeding-related neuropeptides. Therefore, the obesogenic phenotype of offspring from dams fed the high-folate gestational diet can be corrected by feeding them a high-folate diet, showing the post-weaning epigenetic plasticity of the hypothalamus.
ANGPT2 Methylation in CLL  
pp. 720–9

Angiopoietin-2 (ANGPT2) plays a key role in the aggressiveness of chronic lymphocytic leukemia (CLL). High expression levels of ANGPT2 and high degree of angiogenesis have consistently been associated with poor prognosis in CLL. Martinelli et al. have now investigated the DNA methylation status of the ANGPT2 promoter in a large CLL cohort. The authors observed that methylation levels of the ANGPT2 gene inversely correlated with its mRNA expression levels and that a low ANGPT2 methylation status was highly associated with adverse prognostic markers, shorter time to first treatment and shorter overall survival. In two B-cell lymphoma cell lines, ANGPT2 re-expression could be induced by treatment with methyl inhibitors, underscoring the importance of DNA methylation in the transcriptional regulation of this gene.

Blood Glutathione Redox Status and Global Methylation  
pp. 730–8

Oxidative stress and DNA methylation are metabolically linked through the relationship between one-carbon metabolism and the transsulfuration pathway. Under oxidized cellular conditions, enzymes involved in DNA methylation, including DNA methyltransferases and histone deacetylases, may show altered activity. Niedzwiecki et al. found, in a sample of clonal peripheral blood mononuclear cells from Bangladeshi adults, that a more oxidized blood glutathione was associated with decreased global DNA methylation. Interestingly, blood SAM does not appear to mediate this association.

TNS3 Gene Promoter Methylation in Human RCC  
pp. 739–47

Tensin3 is a cytoskeletal regulatory protein that inhibits cell motility. Downregulation of TNS3, the gene encoding Tensin3, in human renal cell carcinoma (RCC) may contribute to cancer cell metastatic behavior. Carter et al. studied the epigenetic mechanisms accounting for TNS3 downregulation. The authors first identified a TNS3 gene promoter containing a CpG island, and quantified the methylation level within this region in RCC samples. RCC DNA showed higher methylation levels (correlating with lower TNS3 gene expression) than both non-tumor kidney DNA and normal control DNA. Importantly, pharmacological demethylation treatment of cultured kidney cells caused a 3-fold upregulation of Tensin3 expression.

Hypermethylation of DNA Repetitive Elements and Early-Onset CRC  
pp. 748–55

Changes in the methylation levels of DNA from white blood cells (WBCs) are putatively associated with an elevated risk for several cancers. Walters et al. have now investigated the association between colorectal cancer (CRC) and the methylation status of three DNA repetitive elements in DNA from peripheral blood. WBC DNA from CRC and matched healthy controls were assessed for methylation across DNA repetitive elements Alu, LINE-1 and Sat2. CRC cases showed a significantly higher median PMR (percentage of methylated reference) for LINE-1, Sat2 and Alu repeats when compared with controls. For each of the DNA repetitive elements, individuals with PMR values in the highest quartile were significantly more likely to have CRC compared with those in the lowest quartile. This association between increasing methylation levels of three DNA repetitive elements in WBC DNA and early-onset CRC is novel and may represent a potential epigenetic biomarker for early CRC detection.

A New Bisulfite-Based Methylation Pattern Profiling  
pp. 765–71

The use of next generation sequencing has expanded our view on whole mammalian methylome patterns. In particular, it provides a genome-wide insight of local DNA methylation diversity at single nucleotide level and enables the examination of single chromosome sequence sections at a sufficient statistical power. Gries et al. now describe a bisulfite-based sequence profiling pipeline, called Bi-PROF, based on the 454 GS-FLX Titanium technology that allows the generation of up to one million sequence stretches at single base pair resolution without laborious subcloning. The authors present a test analysis set of 68 different epigenetic marker regions (amplicons) in five individual patient-derived xenograft tissue samples of colorectal cancer and one healthy colon epithelium sample as a control. Comprehensive methylation pattern interpretation (profiling) assessed by analyzing 105–104 sequence reads per amplicon allows an unprecedented deep view on pattern formation and methylation marker heterogeneity in tissues affected by complex diseases such as cancer.

An Autoradiography Tool for Imaging Class I HDAC Enzymes  
pp. 756–64

Wang et al. evaluated [3H]CI-994, a radioactive isotopologue of the class I HDAC inhibitor benzamide CI-994, as an autoradiography probe for ex vivo labeling and for localizing class I HDAC in the rodent brain. Authors showed that [3H]CI-994 exhibits slow binding kinetics when measured in vitro with isolated enzymes and ex vivo when used for autoradiographic mapping of HDAC1–3 density. The highest HDAC1–3 density was found in the cerebellum, followed by hippocampus and cortex. [3H]CI-994 binding can be dose-dependently blocked with other HDAC inhibitors, including SAHA. This is the first autoradiography tool for imaging class I HDAC enzymes. Whereas the method was validated in the CNS, it could also be applied to other target tissues and used, for example, to evaluate HDAC inhibition when testing novel therapies.