In this issue of Epigenetics

Histone-modifying enzymes are controlled by modulatory protein partner subunits and by other posttranscriptional modifications deposited in the vicinity of the targeted site, creating an intricate network of interactions. Couture and Skiniotis discuss the evolving understanding on the assembly and architecture of histone H3K4 methyltransferase COMPASS complexes and overview the techniques that allow researchers to better define the molecular basis of complex formation and function.

Spp1, H3K4me3 and Meiotic recombination pp. 355–60

In *Saccharomyces cerevisiae*, H3K4me3 is enriched in the vicinity of meiotic double strand breaks (DSBs); nevertheless, the link between H3K4me3 and the meiotic nuclease Spo11 was not known until recently. Now, Acquaviva et al. review the finding that the Set1 Complex PHD-containing subunit Spp1, by interacting with H3K4me3 and Mer2, promotes the recruitment of potential meiotic DSB sites to the chromosomal axis, allowing their subsequent cleavage by the meiotic nuclease Spo11. The authors propose that Spp1 is a key regulator of H3K4 trimethylation catalyzed by Set1 Complex and of the formation of meiotic DSBs. Spp1 not only regulates the catalytic activity of Set1, but also interacts with the deposited mark and mediates its biological effect (meiotic DSB formation) independently of the complex.

Epigenetic Regulation of DACT2 in HCC pp. 373–82

DACT2 is a member of the DACT family involved in the regulation of embryonic development. The human *DACT2* gene is localized in a region of frequent loss of heterozygosity in human cancers. Zhang et al. analyzed genetic and epigenetic changes that affect the regulation of *DACT2* in hepatocellular carcinoma (HCC) cell lines and primary cancer and found no single-nucleotide polymorphism associated with HCC. Among their findings, the authors observed that *DACT2* is frequently methylated in HCC and its expression is regulated by promoter hypermethylation. DACT2 suppresses HCC by inhibiting Wnt signaling in human HCC.

Transcriptional Regulation by Set7 pp. 361–72

In recent years, a number of studies have functionally defined the factors involved in the monomethylation of H3K4 and the regulation of specific genes. In a timely review, Keating and El-Osta now examine how H3K4me is written and what the role of the Set7 methyltransferase is as a key regulatory enzyme mediating methylation of lysine residues of histone and non-histone proteins. The authors systematically explore the regulatory proteins modified by Set7 and highlight mechanisms of specific co-recruitment of the enzyme to activating promoters. With a focus on signaling and transcriptional control in disease the authors discuss specific components of diverse regulatory complexes that mediate chromatin modification and reinterpretation of Set7-mediated gene expression.

NISCH Methylation and Cigarette Smoke pp. 383–88

A putative tumor suppressor gene, *NISCH*, has been shown to be methylated at its promoter in lung tumor tissue as well as in plasma obtained from lung cancer patients. *NISCH* also appears to be more frequently methylated in smoker lung cancer patients than in non-smoker lung cancer patients. Here, Ostrow et al. have investigated the effect of tobacco smoke exposure on methylation of the *NISCH* gene. The authors tested methylation of *NISCH* after oral keratinocytes were exposed to mainstream and side stream cigarette smoke extract in culture. This study indicates that tobacco smoke induces methylation changes in the *NISCH* gene promoter before any detectable cancer. Therefore, examining patients for hypermethylation of the *NISCH* gene may potentially aid in identifying those who should undergo additional screening for lung cancer.

Controlling DNA Methylation by Temperature pp. 389–97

*Myogenin* encodes a highly conserved myogenic regulatory factor that is involved in terminal muscle differentiation. In mammals, methylation of the *myogenin* promoter plays a major role in regulating its transcription. Campos et al. studied the Senegalese sole *myogenin* putative proximal promoter and found that it is highly conserved among teleosts. Therefore, it is plausible that it plays a similar role in controlling *myogenin* expression. The authors found that rearing temperature influenced methylation of the *myogenin* promoter in skeletal muscle of Senegalese sole larvae undergoing metamorphosis. Rearing temperature also affected growth and fast

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Repositioning of nucleosomes facilitates cellular processes, such as transcription and DNA replication, and is likely regulated by several factors. In Zea mays, Mediator of paramutation 1 (Mop1) has been demonstrated to be an epigenetic regulator of gene expression and is likely to function in an RNA-dependent pathway to mediate changes in chromatin. In this issue, Labonne et al. used high-resolution microarrays to assay the distribution of nucleosomes across the transcription start sites of ~400 maize genes in wild type and mutant mop1-1 tissues. The authors identified three genes showing consistent differences in nucleosome positioning and occupancy between wild type and mutant mop1-1 but no direct relationship between the specific changes in nucleosome distribution and transcription. These results also indicate that Mop1 contributions to nucleosome position are not correlated with changes in gene expression, or cooperative with development and other levels of regulation in coordinating gene expression.

**Mop1 and Nucleosome Position**

**Integrated Detection of 5-mC and 5-hmC**

Genome-wide profiling of 5-hmC suggests that 5-hmC may not only be an intermediate form of DNA demethylation but could also constitute an epigenetic mark per se. Here, Xia et al. describe a cost-effective and selective method to detect both the hydroxymethylation and methylation status of cytosines in a subset of cytosines in the human genome. Their results support the idea that hydroxymethylation can regulate key transcriptional regulators with bivalent marks through demethylation and can also affect cellular decisions (such as whether these genes remain active or inactive) upon cellular differentiation. The use of this technology would be useful for uncovering the status of methylation and hydroxymethylation during dynamic biological processes and disease development in multiple biological samples.

**Using NotI-Microarrays in Cervical Cancer**

In this issue, Senchenko et al. investigated genetic and epigenetic alterations in cervical carcinomas using NotI-microarrays containing 180 cloned sequences flanking all NotI-sites associated with genes on chromosome 3. Thirty genes, including tumor suppressors or candidates and genes previously unknown as cancer-associated showed methylation/deletion in 21–44% of tumors. The genes were more frequently altered in squamous cell carcinomas than in adenocarcinomas and a set of seven potential markers is promising for discrimination between the two malignancies.

**MDV Infection and the Regulation of DNMT Genes**

Marek’s disease (MD) is characterized as a T cell lymphoma induced by a cell-associated alpha-herpesvirus, MDV type 1. DNA methylation variations observed during the progression of MD are thought to play an important role in host-virus interactions. Song et al. observed that DNMT3a and DNMT3b were differentially expressed in a chicken MD-resistant line and a MD-susceptible line at 21 days after MDV infection. To better understand the role of methylation variation induced by MDV infection in both chicken lines, the authors mapped the genome-wide DNA methylation profiles in each line using Methyl-MAPS generating datasets that provide a more comprehensive picture of the chicken methylome. Overall, methylation levels were reduced in chickens from the resistant line after MDV infection. The authors also identified infection-induced differential methylation regions and further showed that in vitro methylation levels were associated with MDV replication and that MDV propagation in the infected cells was restricted by pharmacological inhibition of DNA methylation. Therefore, DNA methylation in the host appears to be associated with disease resistance or susceptibility.

**Buccal vs. Blood for EWAS**

Epigenome-wide association studies (EWAS) are associated with a range of issues not typically encountered in genome-wide association studies (GWAS), such as what tissue to analyze. In many human EWAS, it is not possible to analyze the target tissue in large numbers and, consequently, surrogate tissues are employed, most commonly blood. But, is blood more informative than buccal cells are? To assess the potential of buccal cells for use in EWAS, Lowe et al. performed a comprehensive analysis of a buccal cell methylome using whole-genome bisulfite sequencing. Strikingly, a buccal vs. blood comparison revealed six times as many hypomethylated regions in buccal. Most of these regions are not captured by commonly used DNA methylome profiling platforms such as Reduced Representational Bisulfite Sequencing and the Illumina Infinium HumanMethylation450 BeadChip, and also display distinct genomic properties. The authors propose that for non-blood based diseases/phenotypes, buccal will be a more informative tissue than blood for EWAS.