Genomic Med. (2008) 2:147–148
DOI 10.1007/s11568-009-9083-8

ABSTRACTS

HGM2008 cancer and epigenomics symposium abstracts

014: The third dimension of gene regulation: It's all in the looping!

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Compartmentalized distribution of functional components is a hallmark of the eukaryotic nucleus. Technological advances in recent years have provided unprecedented insights into the role of chromatin organization and interactions of various structural-functional components towards gene regulation. SATB1, the global chromatin organizer and transcription factor, has emerged as a key factor integrating higher-order chromatin architecture with gene regulation. Studies in recent years have unraveled the role of SATB1 in organization of chromatin 'loopscape' and its dynamic nature in response to physiological stimuli. The capacity of SATB1 to act at global level presumably stems from its ability to bind a large number of regulatory cis elements. However, only a limited number of SATB1 binding sites (SBSs) have been characterized so far. Genome-wide search for SATB1 targets using the recently derived consensus SATB1 binding sequence (CSBS) yielded large number of CSBS-containing regions including promoters of multiple genes. Using matrix-loop partitioning assay we show that promoters harboring CSBS are differentially present in loop- and matrix-associated regions in Jurkat T cells such that most of the promoters of genes for which SATB1 acted as an activator were found in loop regions whereas those that were repressed by SATB1 were present in the nuclear matrix. Analysis of histone modification patterns at these regulatory regions upon SATB1 knockdown revealed specific changes that correlated well with the expression profiles of respective genes suggesting that SATB1-mediated partitioning could play a role in forging histone modifications characteristic of the expression status of genes. Furthermore, differential SATB1 occupancy upon T cell activation as deduced by ChIP-on-chip analysis resulted in differential expression of SATB1 targets across the human genome. At genome level, SATB1 seems to play a role in organization of the transcriptionally poised chromatin. These studies provide insights into the mechanism of genomic occupancy and distinct modes of transcriptional regulation by SATB1.

015: Fusion gene discovery through transcriptome and rearrangement mapping using ultra high throughput pair end sequencing strategies

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Using gPET pair end strategies, we have mapped to ~100 bp precision, the structural map of the MCF7 breast cancer cell line genome which provides the detailed and comprehensive annotation of all possible genetic rearrangements in this cancer genome. To advance our analysis, we have mapped the MCF-7 transcriptome of ~680,000 full length cDNA clones to the gPET map of rearrangements of the same cell line. Overlaps are considered partially validated rearrangements leading to fusion transcripts. To date, we have identified approximately 450 putative rearrangements that may result in alternative transcripts, with approximately 75 passing the criteria of multiple tags. We have thus performed validation on 20 of these which 10 have been sequenced and shown to have bona fide fusion transcripts as listed below (discovery rate of 50%). Thus far, two fusions have been found in multiple cell lines or primary cancer samples. With this approach, we have developed a clinically achievable digital cytogenetics platform.

016: HP1 proteins from silencing to activation of inducible promoters

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Heterochromatin Protein 1 (or HP1) proteins function as strong transcriptional repressors that preferentially but not exclusively

localize to condensed silenced chromatin. The binding of HP1 proteins to chromatin is in part mediated by conserved chromodomains that specifically recognize the tail of H3 histones methylated on the lysine at position 9 (K9). This binding is unstable and during mitosis, it can be reverted by phosphorylation of H3 on S10 coupled with acetylation on K14. These histone modifications are also observed upon activation of several inducible promoters regulated by the MAP kinase and the NFkappa-B pathways. These modifications also play a role during transcriptional activation by nuclear receptors. We will discuss the role of HP1 proteins in the silencing but also the activation of these promoters and show that HP1 proteins can be part of a mechanism that allows a rapid stimulation of transcription. We will also provide data suggesting that recruitment of HP1 proteins to chromatin is closely linked to the activity of the RNA polymerase II.

017: Epigenetic reprogramming in the mouse

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We have carried out a "sensitized" ENU mutagenesis screen in the mouse to identify genes that modify epigenetic state. We have screened 1,000 F1 offspring for dominant mutations and have identified ten. In all cases they are homozygous lethal, indicating the obligate requirement for the genes that have been hit (Blewitt et al. 2005). So far, we have identified six of the underlying mutations. The remainder have been mapped to between 1 and 3 cM intervals. All tested so far affect expression at epigenetically sensitive loci such as the *agouti viable yellow* allele. Interestingly, in a number of cases the mutations show both paternal and maternal effects, i.e., wildtype offspring from heterozygous mutant parents are different from wildtype offspring from wildtype parents (Chong et al. 2007). Heterozygosity for the mutations is associated with mild abnormal phenotypes. This project has the potential to identify many more novel genes involved in epigenetic phenomena, and to produce hypomorphs and hypermorphs of known modifiers of epigenetic state. These mutant lines will be a valuable resource to study the role of epigenetics in gene/environment interactions. We are now extending the screen to saturation.