Keystone Symposia on Epigenomics and Chromatin Dynamics
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Keystone Symposia kicked off the start of 2012 with two joint meetings on Epigenomics and Chromatin Dynamics and a star-studded list of speakers. Held in Keystone, CO, January 17–22, and organized by Steven Jacobsen and Steven Henikoff and by Bradley Cairns and Geneviève Almouzni, respectively, there was plenty happening in these sessions that it did not seem to matter that the ski-slope conditions were not ideal.

There was a great sense of optimism from the very beginning. The tone was set by Richard Young (Whitehead Institute, MIT), who, in his keynote talk, outlined how the last decade of discoveries and technological advances has taken the epigenetic field to a whole new level. He detailed how our basic biochemical exploration of histones and chromatin has laid the molecular groundwork for stem cell biology, scrutiny of diseases and drug discovery.

A remarkable lineup of speakers followed over the days to come making each session a must see event. I highlight below only some of the talks, which mainly focused on new and different methodologies and the evolution of this rapidly expanding field, but other topics of note from the meeting include chromatin assembly and remodeling, replication dynamics and pioneering work in DNA demethylation.

Reconstruction of Cellular Networks with Genome-wide Functional Annotation

In his talk, Brad Bernstein (Mass General Hospital and Harvard Medical School) detailed two highly complementary studies lead by Manolis Kellis and himself, employing genome-wide functional annotation of the human genome to reconstruct cellular networks. Using ChIP-seq, nine different histone modifications were mapped globally across nine human cell types. Distinct combinations of modifications defined 15 enriched chromatin states, which in turn were used to functionally annotate chromosomal regions. Enhancers show significant cell type-specific signatures whereas promoter states are more stable across cell types.

Promoter and enhancer chromatin states could then be correlated with activities of nearby genes whereby functional gene clusters emerged specific to each cell type. In keeping with cell type-specificity of both enhancer signatures and expression of gene clusters, strong enhancers are particularly enriched for transcription factor (TF) binding motifs recognized by cell type-specific TFs. Strikingly, non-coding, disease-associated SNPs also show enrichment in these cell type-specific enhancer regions and can indeed be linked to diseases involving the particular cell type. By comparing across cell types, insights are gained into transcriptional networks and candidate disease mechanisms that would otherwise have been difficult to elucidate. To further explore the functional significance of these chromatin states, ChIP-seq analyses of 34 known chromatin regulators (CRs) were successfully performed and binding profiles mapped. Interestingly, significant modular co-localization of CRs was observed across cell types. Modules localize to distinct chromatin states, reflect specific histone modification profiles and even associate with coherent gene sets with related functions. Intriguingly, CRs with opposing functions often coexist in the same modules possibly enabling dynamic regulation and fine-tuning of the associated gene clusters.

Increased Epigenetic Plasticity in Tumor Tissues

Andrew Feinberg’s (Johns Hopkins University) talk was focused on the increased epigenetic plasticity associated with the transition from normal to tumor tissue. Comparing numerous normal tissues and corresponding solid tumor samples, Feinberg’s lab identified hyper-variable chromosomal regions named Variably Methylated Regions (VMRs). These are differentially methylated in cancers and often localize to cell cycle and developmental genes. Between individuals, VMR methylation patterns in tumors are much more heterogeneous than those in the parent tissues, suggesting that stochastic methylation events drive tumor development. Importantly, however, a “productive” subset of stochastic outcomes appears to be selected for, as methylation patterns in cancer often resemble patterns of other normal tissues. These observations could tie stochastic methylation events not only to tumor development but also to tissue differentiation and evolutionary adaptation in general. Also, large blocks
of hypomethylated and rare, hypermethylated blocks were found throughout the tumor genomes. These largely overlap with previously described Partly Methylated Domains (PMDs) and Large Organized Chromatin K9 Modifications (LOCKs) containing the majority of known nuclear lamina associated domains (LADs) of the chromosomes.

In her talk, Shelley Berger (University of Pennsylvania) described a correlation between cellular aging and loss of chromatin organization. Senescent human fibroblasts show large chromosomal regions with decreased H3K27 methylation or increased H3K4 trimethylation associated with reduced or increased nuclear lamina binding, respectively. No DNA methylation data was presented. Learning more about sub-nuclear organization of chromatin at a larger scale could ultimately help us understand highly complex multi-factorial processes, such as cellular transformation and aging.

**Relationships between Histone Modifications and Chromatin States**

Whereas correlations between many histone modifications and various chromatin states are well established, the function of these marks is an area of continued debate. Genome-wide studies in yeast by Steve Buratowski’s (Harvard Medical School) and Ollie Rando’s (University of Massachusetts) laboratories were designed to address the roles of H3K4 methylation as well as other modifications. Histone H3K4 di and trimethylation is widely observed over coding regions and highly correlated with gene activity. In both studies, however, loss of either Set1-catalyzed deposition of H3K4 methyl marks or loss of H3K4 methyl “readers” such as Set3 affected only few genes. Of the genes affected, more were de-repressed than repressed and a majority overlapped with non-coding transcripts. Loss of H3K4 methylation in coding regions resulted in cryptic initiation from internal promoters. Likewise, coding genes immediately downstream of non-coding genes were de-repressed. A common mechanism proposed by Rando and Buratowski was H3K4 methylation-directed histone deacetylation. Clearly, care has to be taken when interpreting correlations. Although the presence of a distinct nucleosome signature can have predictive value, the function of a given histone mark is highly context dependent. The better genomes become annotated with cryptic transcriptional elements and non-coding transcripts, the better the functional impact of epigenetic marks and histone signatures is understood.

**Non-coding RNAs and Transcription**

Non-coding RNAs were also at the center of Howard Chang’s (Stanford Medical School) talk. Long non-coding (lnc) RNAs have recently been shown to play a key role in transcriptional regulation. These are capped and polyadenylated and can be transcribed from promoters or enhancers in either sense or antisense direction relative to the nearby coding gene. LncRNAs may function in either cis or trans as guides for chromatin modifiers, as scaffolds, transcriptional enhancers or as decoys with significant impact on cell fate. A large number of lncRNAs localize to cell cycle genes and are differentially expressed in cancers. One example is the 1.5 kb PANDA lncRNA, transcribed from the CDKN1A promoter in parallel with the coding mRNA. Both transcripts are induced with different kinetics by p53 upon DNA damage and are involved in coordinating the cellular response. CDKN1A mRNA translates into the cell cycle inhibitor p21 and PANDA act as a decoy blocking the pro-apoptotic transcription factor NP-YA. Remarkably, a point mutation in p53—occurring in certain cancers—dissociates induction of the two transcripts allowing only the anti-apoptotic PANDA transcript to be formed. Extended analyses of the transcriptome using increasingly sophisticated methods expose a novel network of chromatin regulation in which long distance interactions through non-coding transcripts can transfer chromatin state information from one locus to another without protein translation.

**Meeting Wrap-up**

In conclusion, the chromatin field has broadly benefited from recent advances in molecular imaging, sequencing technology and computational methods giving every reason to join keynote speaker Rick Young in his optimism. Long-range interactions involving enhancers, non-coding transcripts and large chromosomal features are being characterized and linked to cellular function and overall nuclear architecture. Insights are being gained that greatly facilitate the continued exploration of complex, multi-cellular processes such as fetal development, cellular adaptation and aging. At the same time, high-throughput methods allow comparisons of an increasing number of specimens and reveal patterns and concepts that hold big promises for chromatin-based disease diagnostics and therapeutics.

Note

A version of this report appeared previously on line at the Epigenie website (www.epigenie.com).