Meeting report

Chromatin organization and expression

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A report on the 29th Lorne Genome Conference on the Organization and Expression of the Genome, Lorne, Australia, 17-21 February 2008.

The Lorne Genome conference is held annually in the historic seaside town of Lorne on the southern Australian coast. This year's meeting showcased a broad range of topics, including chromatin structure, epigenetic memory, transcriptional regulation and the role of noncoding small RNAs in gene silencing. Here we report on some of the highlights of the meeting.

Chromatin dynamics and transcription regulation

There is now strong evidence for the role of noncoding RNA, particularly microRNA (miRNA), in establishing and maintaining the transcriptional state of the chromatin. Michael Axtell (Pennsylvania State University, University Park, USA) described new molecular and computational biology techniques to screen for novel small RNAs and their functions in plants. He and his colleagues applied high-throughput 'degradome' sequencing and directly identified miRNA targets using experimental data. In addition, they recognized molecular functions for several other types of small RNAs in various plant species. Interestingly, they showed that diverse miRNA sequences from different plant species can perform common biological functions.

Posttranslational modifications of histones form the histone code that modulates transcription by affecting histone-DNA interactions and recruiting other transcriptional activator and repressor proteins. One of the more memorable talks at the meeting concerned chromatin organization and modification by David Allis (Rockefeller University, New York, USA). Allis described how effector proteins have the capacity to recognize histone tail posttranslational modifications through protein motifs such as the bromodomains that specifically recognize acetylated lysine residues. In particular, he described how certain PHD finger domains, which bind specifically to trimethylated lysine marks on histone H3, have recently been identified as 'readers' of this mark. It is generally thought that such motifs recognize posttranslational modification and create a network of interactions that decipher the histone code. Importantly, however, Allis also discussed recent questioning of the validity of a simple one-mark-to-one-module type of decoding and the need for a modified histone code hypothesis that can accommodate both observations that multiple binding partners have been reported for a single histone, and that bromodomains are promiscuous with regard to the sequence context of substrate acetylation marks. He proposed the "phenomenon of multivalency, in which the cooperative engagement of several linked substrates by a species with more than one discrete interaction surface" may be a common mechanism in chromatin transactions and account for the above issues "without abandoning the core of the original histone code hypothesis."

Kenneth Zaret (Fox Chase Cancer Center, Philadelphia, USA) reported an interesting mechanism whereby chromatin opening by 'pioneering' transcription factors precedes histone modifications during tissue-specific gene activation. He and colleagues established the ability of the FOXA transcription factors to recognize highly compact silent genes that have the potential to be activated in developing liver cells. They showed that FOXA factors have non-sequence-specific, intrinsic binding capacity to highly condensed chromatin and are able to expose the underlying DNA. They used the fluorescence recovery after photobleaching (FRAP) technique to demonstrate that FOXA factors may laterally scan along the chromatin and serve as an epigenetic mark to indicate chromatin identity and potential activity. Indeed, the notion that transcription factors themselves can serve as critical epigenetic marks has been lost with the excitement of the histone code hypothesis.

Steve Smale (University of California, Los Angeles, USA) provided a functional support for such pioneering transcription factors in the transcriptional activation of tissue-specific genes in differentiating embryonic stem (ES) cells. He reported the presence of selective unmethylated regions in the enhancers of well-defined tissue-specific genes that are maintained as unmethylated in ES cells owing to the binding of specific pioneering transcription factors. Erasure of these enhancer marks in differentiated cells led to assembly of repressive chromatin structures that were resistant to decondensation. The data suggest that these enhancer marks in ES cells are important for subsequent transcriptional activation of genes in differentiated tissues.

Continuing with the theme of regulatory changes in the composition of chromatin, Robert Kingston (Harvard Medical School, Boston, USA) described a new technology for isolating locus-specific chromatin and associated interacting proteins. He has used a modified fluorescent *in situ* hybridization protocol to isolate human telomere-specific chromatin. He and his colleagues compared telomeres from HeLa cells with those from cancer cells that employ alternative lengthening of telomeres (ALT) and discovered a family of orphan nuclear receptors that bind specifically to ALT telomeres. Kingston reported that the interaction with these proteins is required for mediating the recombination needed to maintain ALT telomeres.

Cancer genomics

Molecular events underlying gene regulation in cancer were the major focus of talks given by Susan Clark (Garvan Institute for Medical Research, Sydney, Australia) and David Bowtell (Peter MacCallum Cancer Centre, Melbourne, Australia). Clark focused on understanding the interplay between DNA methylation and chromatin modifications and their contribution to aberrant gene expression in cancers. She described a genome-wide screen for differential DNA methylation aimed at identifying patterns of CpG hypermethylation in colorectal cancer samples. In this study she identified a novel mechanism for epigenetic gene silencing involving coordinated silencing of large regions of chromosomes, which ensures the simultaneous suppression of numerous genes regardless of their individual methylation status. Many cancer epigenome studies have focused on locus-specific changes, but Clark's work emphasizes the fact that the global consequences of these epigenetic changes must be considered.

Bowtell described a large cohort study (the Australian Ovarian Cancer Study) that addresses epidemiological and genetic aspects of ovarian cancer. He and his colleagues have carried out genomic analyses of 330 ovarian cancer samples, profiling regions of chromosomal DNA duplication or loss and patterns of gene expression. In the process they have created one of the largest expression datasets for ovarian cancer so far. From the expression data they were able to identify four molecular subtypes of high-grade serous and endometrial cancer, as well as two smaller invasive subtypes reflective of borderline serous and low-grade endometriod cancers. They are currently investigating mutations that drive the development and growth of ovarian tumor subtypes.

Regulatory networks, nuclear organization and epigenetic reprogramming

Characterization of transcription factor-DNA interactions into regulatory networks is important for understanding differential regulation of gene expression. Marian Walhout (University of Massachusetts Medical School, Worcester, USA) presented a systematic approach to identifying transcription factor-DNA and factor-factor interactions and incorporated them into regulatory networks using freely available Web-based packages. She used a modified yeast one-hybrid assay to identify transcription factor-DNA interactions between *Caenorhabditis elegans* gene promoters and transcription factors, and the networks that connect them. Conversely, Sean Grimmond (University of Queensland, Australia) and colleagues reported a novel way to map regulatory networks by surveying the transcriptional output in a model system of ES cell differentiation. They used transcript shotgun, cap analysis gene expression (CAGE) and small RNA sequencing of mouse genome to determine the activity and transcriptional complexity of the whole genome. They subsequently identified thousands of new protein-coding transcripts and established pathways and genetic networks that control ES differentiation.

Defects in genome organization and nuclear architecture are associated with various human diseases, including cancer. Tom Misteli (National Cancer Institute, Bethesda, USA) discussed how intranuclear chromosome positioning is a determining factor in the formation of cancer translocations. His group has developed and used an experimental system to examine how double-strand breaks (DSBs) are recognized *in vivo* and how DNA damage response pathways are activated in the context of chromatin. In this system, DSBs can be induced at a defined genomic site and monitored in real time in living cells. He presented data showing that chromosomes are organized in nonrandom higher-order spatial locations within the nucleus and that physical proximity of chromosomes contributes to the formation of translocations. In line with this interpretation, his group finds that broken chromosome ends maintain their position and generally only undergo translocations with neighboring DSBs. Remarkably, using this same system, Misteli reported that their data strongly suggest that the cellular DNA damage response can be activated in the absence of DNA damage.

Epigenetics is the study of heritable changes in gene expression that occur in the absence of changes in the

underlying DNA sequence. Emma Whitelaw (Queensland Institute of Medical Research, Herston, Australia) described a mutagenesis screen using ethylnitrosourea for modifiers of epigenetic reprogramming in the mouse. In this screen, an erythroid-specific green fluorescent protein (GFP) transgene that is sensitive to perturbations in the epigenetic machinery was used to isolate dominant mutations that varied the expression of the GFP reporter. Several of these mutations were confirmed to be involved in epigenetic regulation by their ability to affect the expression of the endogenous gene *agouti viable yellow*, a well-known locus with epigenetic variability.

In conclusion, genome regulation requires coordination of various regulatory mechanisms, including transcriptional regulation, chromatin remodeling and nuclear organization. By showcasing speakers from the most innovative research groups in the field, the meeting created an electrifying atmosphere as discoveries pivotal to modern genome biology were reported.

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