Genome **Medicine**

MEETING REPORT

Generalizing complexity: a fruitful partnership of functional genomics and systems biology

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Abstract

A report on the meeting 'Functional Genomics and Systems Biology 2011', Wellcome Trust Conference Centre, Wellcome Trust Genome Campus, Hinxton, Cambridge, UK, 29 November to 1 December, 2011.

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Despite of the astounding complexity of biological systems, the history of biology is marked by attempts to discern generalizable principles. Functional genomics and its ultimate integration with systems biology remain pivotal to enabling advances in experimental technology that provide detailed and comprehensive information about networks of biological interactions. The Functional Genomics and Systems Biology 2011 conference focused on recent, largely unpublished developments in sequencing-based approaches and computational methods, including their application to chromatin and proteome systems biology. Experts at the meeting also discussed advances in translating these findings to the clinic, with the ultimate goal of promoting personalized medicine. Here, we summarize some of the highlights presented at this exciting conference.

Yeast leads the way in systems biology

A relatively simple genome and the availability of powerful methods for their genetic manipulation make yeast models the central paradigm in systems biology. Brenda Andrews (University of Toronto, Canada) presented the latest applications of synthetic genetic array (SGA) technology to proteome localization, allowing quantitative determination of subcellular localizations for the majority of yeast proteins. Published work from the laboratories of Andrews and Charles Boone (University of Toronto, Canada) exploited the SGA method to produce a genome-scale landscape of genetic interactions in *Saccharomyces cerevisiae*. Integration of this technology with high-content microscopy screening of a green fluorescent protein fusion library allowed construction of abundance localization networks across the yeast proteome, including flux networks of dynamic protein localization changes. Frank Holstege (University Medical Center Utrecht, The Netherlands) emphasized the importance of specificity and redundancy in understanding regulatory processes. Work in his laboratory employed gene expression changes in *S. cerevisiae* upon single or double deletion of 165 chromatin machinery components to build a global network of chromatin interaction pathways, characterized by remarkably specific effects on gene expression for a majority of chromatin regulators. A similar analysis focused on kinase/phosphatase deletions revealed general principles of redundancy in signaling networks. Holstege argued that the majority of genetic interactions are non-intuitive and underlie a combination of partial redundancy and regulatory coupling, allowing a single node in the network to couple/uncouple two distinct responses.

Jurg Bahler (University College London, UK) and Simon Tavaré (University of Cambridge, UK) also presented interesting technological developments in yeast. Bahler's talk focused on a quantitative comparison of the fission yeast transcriptome and proteome using nCounter/RNA-Seq and liquid chromatography-tandem mass spectrometry (LC-MS/MS), and provided quantitative support for previously noted differences in mRNA/long noncoding RNA average abundance, as well as a much higher abundance and dynamic range for proteins. Correlation of protein/mRNA abundance additionally suggests that there is considerable scope for translational (in addition to transcriptional) control. Tavaré presented a detailed model of yeast replication dynamics based on time-course chromatin immunoprecipitation sequencing (ChIP-Seq) analysis of G1-synchronized yeast cells labeled with bromodeoxyuridine.

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Functional genomics and systems biology unite in metazoan systems

In contrast to the more traditional static snapshots of cellular state, several speakers at the conference discussed novel functional genomics approaches to explore and rationalize biological heterogeneity. We and others are exploiting ChIP-Seq and RNA-Seq to understand the evolutionary principles of regulatory divergence across transcription factors (TFs) and non-coding RNAs. Based on modeling of high-throughput RNA interference (RNAi) screening, Chris Bakal (The Institute of Cancer Research, UK) elaborated on a model of morphogenesis as a switch-like, versus continuous, transition between stable morphological states (analogous to molecular conformations). Sarah Teichmann (MRC Laboratory of Molecular Biology, UK) presented detailed analyses of RNA-Seq data in mouse Th2 cells that show a bimodal gene expression distribution of protein-coding genes indicative of putatively non-functional lowly expressed genes and functional highly expressed genes. Mike White (University of Manchester, UK) discussed the related concept of cell-to-cell heterogeneity and its effect in transcriptional responses, revealed through extensive biochemical studies and simulations based on single-cell observations. These findings argue for an important biological role of transcriptional heterogeneity and precise control of oscillatory cellular dynamics, which likely contribute to population robustness by mitigating the effect of temporal fluctuations in paracrine signaling.

A major highlight of the conference was the presentation of insightful works that employed functional genomics to build systems biology models of metazoan transcription, moving beyond the yeast system. Ido Amit (Weizmann Institute of Science, Israel) presented unpublished work on the development and validation of an Indexed high-throughput ChIP-Seq method (iChIP) to study dynamic occupancy of 40 transcription factors during stimulation of mouse dendritic cells with the toll-like receptor agonist lipopolysaccharide, thereby modeling their transcriptional response to pathogens. Among the insights made by this work is a model of a layered transcriptional regulation in three levels: organizers (pioneering TFs), controlling chromatin accessibility, primers (control of basal expression levels) and transducers (dynamic DNA-binders in response to stimuli). Building on published efforts to model enhancer activity from TF occupancy during *Drosophila melanogaster* mesoderm development, Eileen Furlong (European Molecular Biology Laboratory, Germany) presented a method that facilitates cell-type-specific ChIP-Seq based on fluorescence-activated cell sorting of covalently cross-linked transgenic embryos. Integration of information on histone modifications and polymerase II occupancy with a large collection of developmental enhancers of known

activity has led to predictive models and uncovered general principles of the relationship between TF occupancy and chromatin marks at dynamically activated enhancers. Phil Arnold (University of Basel, Switzerland) discussed published work within the FANTOM Consortium (http://fantom.gsc.riken.jp/) on modeling of gene expression dynamics during monocyte differentiation as a linear function of predicted transcription factor binding sites (TFBSs). Arnold presented the adaptation of this method to modeling of genome-wide profiles of chromatin marks in terms of predicted TFBSs; this points to candidate regulators for recruitment of specific chromatin modifications (for example, H3K27me3).

A number of talks in the meeting addressed regulatory aspects beyond transcription, suggesting additional scope for regulation. Lars Dolken (Cambridge University, UK) elaborated on the kinetics of RNA processing as inferred from a combination of progressive 4-thiouridine tagging and RNA-Seq. Results have pointed to several classes of splicing kinetics for coding and non-coding RNAs, including remarkably inefficient processing of small nucleolar RNAs. Piero Carninci (RIKEN Yokohama Institute, Japan) presented published and ongoing work from the FANTOM Consortium that extensively exploits Deep cap analysis of gene expression (DeepCAGE) technology for transcriptome analysis. Time-course analysis of a panel of a hundred primary cells revealed submodalities of promoter architecture associated with tissue-specific transcription (enrichment of TATA promoters) versus ubiquitous expression (mostly CpG promoters). Carninci's results also explored dynamic and spatial expression of repeat elements, pointing to preferential retrotransposon (LINE and SINE repeats) expression in nuclear fractions and a role for SINEs in regulation of protein synthesis.

Moving towards personalized medicine

About a third of the talks in the conference discussed recent applications of functional genomics to various pathological settings, including complementary approaches to genome-wide association studies, such as employing gene and protein networks for identification of candidate disease genes (Thomas Schlitt, King's College London, UK) and the use of functional interaction networks for drug target identification (Nicola Mulder, University of Cape Town, South Africa). Keith Baggerly (MD Anderson Cancer Center, USA) stressed the scientific and ethical importance of reproducibility and rigorously controlled bioinformatics in high-throughput biology, even more so for research that may eventually lead to clinical trials. Of particular originality and scientific implication was Michael Snyder's (Stanford University, USA) presentation on his own personal profile followed over a 21 month period using an integrated 'omics approach; his profile

included normal and virally infected states. This pioneering study integrated genome sequencing with profiling of the epigenome, transcriptome, proteome, metabolome, autoantibodiome and microbiome to correlate heteroallelic expression with disease state. The results illustrated the potential of integrated functional genomics to predict disease risk, with important implications for the ultimate development of personalized medicine.

Towards convergence of functional genomics and systems biology

As the cost of sequencing continues to drop and related technologies develop, increasingly comprehensive studies based on functional genomics are becoming feasible. A major challenge remains in adequately and reproducibly adapting analysis and biological interpretation efforts to the vast amounts of datasets generated. Nevertheless, groundbreaking work presented at this exciting conference exemplified the current potential of these approaches to produce systems biology models of biological interactions, explore sources of biological heterogeneity and emerging regulatory mechanisms, and inform disease prognosis and outcome, potentially tailoring predictions to each individual.

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