Meeting report

Living on the edge

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A report on the Second EMBL/EMBO Symposium on Functional Genomics: 'Exploring the Edges of Omics', European Molecular Biology Laboratory (EMBL), Heidelberg, Germany, 16-19 October 2004.

EMBL's recent symposium on functional genomics showed how this new field has matured. Work from a broad range of model organisms provided new biological insights, and a plethora of improved high-throughput technologies promised more of these in the future. We focus here on biological networks - a major theme of the meeting.

Network motifs

The identification of patterns in biological data can uncover mechanisms through which processes are regulated. Uri Alon (Weizmann Institute of Science, Rehovot, Israel) presented evidence that in gene-regulatory networks particular patterns of interconnections (network motifs) are enriched when compared to a randomized network. For example, the three-node feed-forward loop, in which transcription factor X regulates transcription factor Y and both jointly regulate gene Z, is a frequently used network motif; one example is in the L-arabinose utilization system in *Escherichia coli*. Studying this system *in vivo* Alon found that the feed-forward loop is protected against fluctuation of external signals and allows rapid shutdown of transcription. The identification of network motifs is important, as they are thought to perform specific information-processing tasks.

Dissecting networks involved in complex contexts such as animal development is a monumental task. Norbert Perrimon (Harvard Medical School/Howard Hughes Medical Institute, Boston, USA) reported how his group is starting to tackle network complexity by carrying out genome-scale loss-of-function analysis in *Drosophila* cells using RNA interference (RNAi). The strategy is to perform multiple RNAi screens in different defined contexts (different cell lines or different stimuli) using sensitive and reliable reporter assays. Perrimon focused on canonical signaling pathways such as those involving Jaks and Stats, Wingless (Wg) and Hedgehog. From these systematic screens it appears that there are important overlaps between the pathways, and that the signaling components forming these pathways, are more numerous than expected. These findings were illustrated in a network topology map where, for example, 32 components are shared in the Wg and Hedgehog screens, but only two are shared between Wg, Hedgehog and Jak-Stat screens. To try and organize the data, a phenoprint matrix (a color-coded matrix that visually links phenotypes to genes) is being built, which at the moment encompasses about 20 genome-wide screens and more than 7,500 genes. This impressive work showing unexpected connections challenges our current view of how signal information is transduced to form an appropriate response.

An important role of biological networks is transcription regulation. Understanding how DNA-binding transcriptional regulators interpret the genome's regulatory code is essential. Richard Young (Whitehead and Broad Institutes, Massachusetts Institute of Technology, Cambridge, USA) reported the use of genome-wide location data (ChIP-chip) combined with phylogenetic conservation data to describe the promoter architecture and the global behavior of transcription factors in *Saccharomyces cerevisiae*. Four types of architectures were found: single regulators; repetitive binding motifs; multiple regulators; and co-occurring regulators. There are also four global behaviors: condition invariant (the transcription factor binds the same targets regardless of the environment tested); enabled (the transcription factor does not bind its target until enabled by the environment); expanded (the binding pattern is expanded by changes of environment); and altered (different targets

depending on the environment). Of particular interest, it was estimated that 17% of DNA-binding factors are found on specific targets but wait for a signal before regulating transcription. This work will provide an excellent framework for modeling global gene expression in other eukaryotes.

Network hubs

Networks have particular nodes that are more highly connected than others; these nodes are called hubs. Marc Vidal (Dana-Farber Cancer Institute, Harvard Medical School, Boston, USA) described the use of large-scale yeast two-hybrid mapping to derive a protein-interaction network in which he found two types of hub, which behave differently. The first type is called the 'party' hub, and has numerous partners that interact with it simultaneously. The second type is the 'date' hub, which also has many potential partners, but where the interacting partners depend on location and time. The date hubs represent high-level connectors between structural or functional modules such as cellular organelles or particular pathways, whereas party hubs function inside these modules, at a lower level. In yeast, for example, calmodulin is a date hub that connects four different modules, while one of these modules, the endoplasmic reticulum, forms a party hub.

Stuart Kim (Stanford University, USA) has uncovered hubs through analyzing DNA microarray data for conserved gene co-regulation. These hubs, which he calls 'subunits' and 'integrators', also have different properties: subunit components are highly interconnected whereas integrator hubs have a central connection point with few connections between components. Also, subunit components are usually essential, whereas most integrator components are not, suggesting that these latter proteins may have partially redundant functions. He also presented evidence that newly evolved genes are not found in hubs. The uncovering of different properties for different types of hub is fundamental for further studies of biological networks.

The microRNA network

MicroRNAs (miRNAs) regulate gene expression and are found in all metazoans studied so far. Three presentations addressed different aspects of miRNAs: identification of their targets; identification of novel miRNAs; and analysis of their biological functions. Steve Cohen (EMBL, Heidelberg, Germany) presented the results of systematic *in vivo* analysis of miRNA/target pairing characteristics in *Drosophila*. It was determined that the 5′ end of the miRNA is the most important in pairing and that a minimum of seven pairing nucleotides is required for silencing. Three types of target were also identified: canonical (perfect pairing), seed (fork-like) and compensatory (bubble-like). He estimated that half of the genes in the genome are regulated through miRNAs.

How miRNAs work is still not entirely defined. Ronald Plasterk (Hubrecht Laboratory, Utrecht, The Netherlands) has used RNAi in *Caenorhabditis elegans* to identify genes required for miRNA function. His laboratory used a reporter gene (*lin-14::lacz*) that is regulated by the miRNA *let-7*. In this system, when *let-7* becomes expressed, the level of expression of the protein LACZ diminishes because of a translational inhibition of the reporter gene. Using a candidate-based approach that relies on previous genome-wide RNAi screens, 508 genes were tested by RNAi for causing an absence of silencing; 25 new genes were found with this property, one of which is the gene encoding the small ubiquitin-like modifier protein SUMO.

Victor Ambros's laboratory (Dartmouth Medical School, Hanover, USA) is studying the biological function of miRNAs by generating deletions of the miRNA genes in *C. elegans*. He described how, by studying miRNA loss-of function phenotypes, miRNA activities have been grouped into four classes: coordinated (repression of multiple targets); collaborative (multiple miRNAs acting on common targets); redundant; and modulated. Redundancy within the *let-7* family was shown; double mutants between the two *let-7* family members *mir-48* and *mir-84* display a phenotype, but the single mutants do not.

The meeting was inspiring, presentations were of very high quality and participants were able to interact in a relaxed and comfortable atmosphere. The field of functional genomics has truly become 'functional' and we can look forward to hearing more at the next symposium.

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