Meeting report

From single cells to whole organisms

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A report on the European Science Foundation Conference 'Functional Genomics and Disease', Oslo, Norway, 6-10 September 2005.

Functional genomics aims to provide a bridge from the static information in the genome to the related functional properties of the cell, tissue or organism. Data on a genome-wide level are generated using a variety of high-throughput technologies, and are analyzed using bioinformatics and system-level integration. The program of the recent European Science Foundation Conference on functional genomics linked the most promising developments in functional genomics research and technology with their applications and future in biomedicine.

Complex genotype-phenotype relationships

Considerable effort is currently being made to reveal the relationship between complex genotypes and phenotype, for example, in looking at the enormous genetic variation that exists in outbred populations such as our own and how it manifests itself in phenotypic variation. One approach to uncovering the molecular basis of common diseases such as cancer and cardiovascular diseases is the correlation of sequence variation among healthy and ill individuals to try and understand how genetic perturbations interact to affect clinical outcome. Analyzing genotype-phenotype relationships in simpler organisms than humans, Charlie Boone (University of Toronto, Canada) and Andrew Fraser (Wellcome Trust Sanger Institute, Cambridge, UK) reported on global genetic-interaction projects in *Saccharomyces cerevisiae* and *Caenorhabditis elegans* that aim to identify overlapping functions and compensatory pathways that complicate the phenotype. Using an automated screen for suppressor/enhancer mutations, Boone's group analyzed 250,000 mutants of *S. cerevisiae* for synthetic genetic sickness or lethal genotypes, which are important for understanding how an organism tolerates random mutation. Interestingly, the genetic-interaction map appears to be four times as complex as the protein-protein interaction map. Genetic interactions do not overlap with physical interactions, but predict functional neighborhoods and clearly identify components of pathways whose order of action remains to be determined.

Fraser described an RNA interference (RNAi) approach to the construction of a genetic-interaction map, using *C. elegans* fed on bacteria expressing double-stranded RNA (dsRNA). The map was based on 200,000 experiments, in which each gene was tested against every other one. Most interestingly, genes involved in chromatin remodeling have the highest number of interactions and modulate weak mutations in other genes, such that chromatin-remodeling genes function as phenotypic buffers. A future challenge will be to transfer this knowledge to humans. RNAi knockdown experiments in mammalian cells should provide further insights, as described by René Bernards (Netherlands Cancer Institute, Amsterdam, The Netherlands). Using this technology, he has identified the cylindromatosis tumor suppressor gene (*CYLD*) as a regulator of the anti-apoptotic transcription factor NFκB. The link with NFκB suggested the possibility of treating cylindromatosis, a tumor of skin appendages such as sweat glands, with aspirin, because aspirin prevents activation of NFκB and thus could suppress the cell proliferation. Indeed, Bernards reported the finding of disease regression in a clinical trial of topical application of aspirin cream.

Protein function, interaction and signaling

Two thirds of all the coding sequences from completed genomes have been assigned to only 1,400 known domain families, and this enables ancient evolutionary relationships to be determined. About 200 of these domain families are common to all kingdoms of life and new protein functions have evolved through domain duplication and shuffling. Christine Orengo (University College London, UK) presented a

bioinformatics perspective on how functionally related protein families extend or decrease in size in a correlated manner within any given species: examples are the DNA topoisomerases and the elongation factor G (EF-G) family. Considering that 80 genomes have been completely sequenced, phylogenetic occurrence profiles now provide an additional tool to extend their functional annotation. Using data obtained by mass spectrometry and peptide arrays, Tony Pawson (Samuel Lunenfeld Research Institute, Toronto, Canada) pointed out that small alterations in peptide motifs and motif shuffling can influence the activation and function of signaling proteins. For instance, single amino-acid substitutions can alter the binding specificity of SH2 domains. This apparent flexibility might have had an evolutionary advantage in the sense that the binding specificity of SH2 domains might be able to change rather rapidly, thus allowing the formation of new signaling connections as animals became more complex.

Signaling that leads to the induction of new gene expression enables cells to adapt to environmental changes or, in the case of cell-cell communication, plays a major role in biological processes such as the regulation of embryonic development. One intriguing example of how quantitative changes in the level of a particular signaling molecule can interfere with morphological development was presented by Irma Thesleff (University of Helsinki, Finland) in the context of tooth development in mice. The development of these ectodermal appendages starts from tooth placodes (thickened plates of ectoderm) and is regulated by interactions between epithelium and mesenchyme. The epithelial structures called enamel knots, which regulate the morphogenesis of the tooth crown enamel, represent signaling centers and express commonly used developmental signaling molecules such as bone morphogenetic proteins (BMPs), fibroblast growth factors (FGFs), Sonic hedgehog, and Wnt proteins. Thesleff reported that Ectodin, a secreted BMP inhibitor, is expressed in a complementary pattern to enamel knots in developing teeth. Ectodin-deficient mice have enlarged enamel knots, highly altered cusp patterns on the teeth, and extra teeth. Unlike the situation in normal teeth, excess BMP accelerates the developmental patterning process in Ectodin-deficient teeth. Thus, modification of the levels of cell-cell signaling molecules affects morphology.

From bench to bedside

The brain is the most complex organ in the body and allows us to interact with the world around us. Unlike many other tissues, central nervous system neurons are not routinely replaced or repaired, and when neurons are lost because of trauma or disease there is often severe loss of function. Because of the cellular complexity of the nervous system, neuronal death involves many signaling pathways, the death of one neuron affects another, and injury because of cell death develops over time. Valina Dawson (Johns Hopkins University, Baltimore, USA) discussed research ranging from the inhibition of cell death to preconditioning (using short periods of ischemia to make the brain more resistant to a subsequent ischemic insult) and neuroprotection. Dawson described large-scale gene-expression experiments that identified the gene *iduna*, a potential new key player in the preconditioning process and a possible 'druggable target'. *Iduna* knockdown in mice inhibits the neuroprotective effect of preconditioning at a cellular level, whereas its overexpression increases the protective effect. Even if it is still a long way from bench to bedside, this is a clear example of the ongoing translation from research to clinic.

Most disease-related molecular studies focus on the analysis of the affected organ, tissue or cell. Much of this material is, however, difficult to access in a routine clinical setting and is therefore of limited value for diagnostic testing. On the other hand, venipuncture or bloodletting was flourishing well before Hippocrates' time and blood is one of the easiest tissues to access and examine in the laboratory. During its circulation, the blood picks up proteins from all organs and thus blood serum can be used as a window into the state of the tissues of the body. Ruedi Aebersold (Swiss Federal Institute of Technology (ETH), Zurich, Switzerland) presented a pioneering study showing the overlap of 3,203 *N*-glycosylated peptides isolated from blood serum with various tissues such as liver, breast, lung and brain. Although the identification of tissue- and disease-specific protein markers is still in progress, the analysis of serum proteome patterns opens a new window on the remote sensing of tissue stages and changes within the body.

System-level integration

Understanding the mechanisms that sustain living systems has always been the ultimate goal in biology, and solutions are now coming from the relatively new discipline of systems biology. The essence of systems biology lies not in computational power or high-throughput analysis: it is all about dynamics, the quantitative analysis of biological processes over time and space. Thus, systems biology seeks to explain biological phenomena not on a gene-by-gene basis but through the interaction of all the individual components in a cell or organism. As Aebersold remarked, systems biology is the study of the syntax of biological information, like choosing the right number of words and putting them in the right order. Olaf Wolkenhauer (University of Rostock, Germany) reviewed recent approaches to mathematical modeling and the simulation of fundamental dynamic processes such as gene expression and cell signaling, and pointed out that the intracellular location of components can induce a time delay in their actions that has been ignored in modeling so far. For example, the need for transport into the nucleus produces a delay between the activation of the extracellular signal-related kinase by phosphorylation in the cytoplasm and its activity in phosphorylating transcription factors within the nucleus.

To enable sophisticated biological and computational approaches, new molecular tools for high-throughput analysis and even single-molecule detection and quantitation are currently being developed. Ulf Landegren (Uppsala University, Sweden) described a set of such tools, namely the circularizing nucleic acid probes known as 'padlock' probes, proximity ligation and rolling-circle amplification assays, which can be applied to the quantification of very large sets of molecules in solution or *in situ* on a single-cell level. In these applications, the probe molecules used to detect DNA, RNA or proteins are in the form of short DNAs that circularize on binding their target and are then amplified by rolling-circle replication.

The meeting covered a wide range of topics, from single cells to whole organisms, and clearly demonstrated that functional genomics is a growing interdisciplinary field. The future will undoubtedly show an increasing impact of functional genomics on disease-related research.