Meeting report

Metabolomics shows the way to new discoveries

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A report on the First Annual Meeting of the Metabolomics Society, Tsuruoka, Japan, 20-23 June 2005.

Since the 1950s the central dogma of molecular biology has been a linear conception of the cell where the general flow of information goes from gene to transcript to protein. Enzymes encoded by the genes then affect metabolic pathways and lead to changes in the phenotype of the organism. This traditional thinking is no longer accepted, however, and cellular processes are in reality organized into interlocking networks, with many feedback loops, and should rather be represented as dynamic protein complexes interacting with neighborhoods of metabolites. The construction, visualization and understanding of these metabolic networks, whose variables constitute the metabolome, is certainly a major challenge for systems biology, as is a full understanding of the fluxes through metabolic neighborhoods and their control.

The analysis of the metabolome drew nearly 300 academic and industrial scientists together this summer at the Tsuruoka Town Campus of Keio University, in Japan, for the first annual meeting of the recently formed Metabolomics Society [http://www.metabolomicssociety.org]. Some were interested in the many technological developments that are needed for metabolomics, while others were involved in the integrative analyses of the metabolome (with proteomics and transcriptomics) to generate predictive and hypothesis-generating mathematical models with the aim of better understanding the cell at the systems level. The application of metabolomics spans the human, plant and microbial sciences, and there were many presentations on the search for metabolite biomarkers that can serve as indicators of disease progression or response to therapeutic intervention.

The metabolome comprises the quantitative complement of all the low-molecular-weight molecules present in cells in a particular physiological or developmental state. The measurement of the entire metabolic pool is one goal for metabolomics. Major challenges when measuring the metabolome are posed by its chemical complexity and the heterogeneity of metabolites, and the wide dynamic range of these biochemical species. Thus there is a need to develop parallel, high-throughput analyses. An insight into one approach was presented by Tomoyoshi Soga (Institute for Advanced Biosciences, Keio University, Tsuruoka, Japan) who described studies using capillary electrophoresis, which separates metabolites on the basis of their charge and size. Once separated, the metabolites are detected using time-of-flight mass spectrometry (TOF-MS). Using this approach to identify and measure both anionic and cationic analytes, Soga claimed that around 80% of the metabolites in *Escherichia coli* can be accurately quantified, and one can perhaps envisage that the remainder will become 'visible' to capillary electrophoresis after appropriate derivatization.

Classic studies in microbial metabolism used radioactively labeled substrates to define new metabolic pathways. It is therefore not surprising that similar strategies using substrates labeled with heavy isotopes, which can be detected by mass spectrometry and nuclear magnetic resonance (NMR), are now being used for pathway discovery. What is surprising is the interconnectivity of previously unrelated pathways revealed by these studies. This was the subject of Henri Brunengraber's (Case School of Medicine, Cleveland, USA) fascinating account of pathway discovery by the association of metabolomics and mass analysis of isotopomers (isotopic isomers). Brunengraber's strategy was to use isotopomers of metabolites generated by labeling with a variable number of heavy atoms in specific positions. The fate of these labeled metabolites can be readily assayed by mass spectrometry of metabolite extracts from, for example, rat livers that had been perfused with labeled metabolites. His presentation demonstrated how this approach could be used to identify unknown reactions between ostensibly completely different pathways, which would have been missed without the use of

specific substrate labeling. Similar studies using tracer-based metabolite profiling were also detailed by Paul Lee and Laszlo Boros (Harbor-UCLA Medical Center, Torrance, USA). Lee discussed the cellular response to a precursor in terms of specific changes in the direction and magnitude of the redistribution of metabolic intermediates, and showed how tracer-based metabolomics can be used to follow this. Boros showed a more specific example of the same approach, which is termed SIDMAP (stable isotope-based dynamic metabolic profiling). It was applied to mutation analysis in human fibroblast cell lines that led to the identification of changes in metabolic networks after pulsing cells with a labeled D-glucose tracer.

Integrative biology was the theme of the talk by Bernhard Palsson (University of California, San Diego, USA), who described his group's work on the plasticity of the *E. coli* metabolome during adaptive evolution. Palsson reviewed some of the team's pioneering work on network biology using constraint-based modeling, and also described more recent work on the estimation of kinetic parameters from metabolic networks using a method involving so-called *k*-cones. The core of this work comprises experiments in which *E. coli* K-12 MG1655 is taken through a series of defined adaptive stages to increase the production of lactic acid. During the evolutionary process the organism's genome was resequenced to identify mutational changes, and these changes were correlated with changes in metabolite levels.

Part of the meeting was devoted to a discussion on standards for metabolomics experiments. Given the chemical diversity of metabolites, the multitude of analytical platforms needed for their accurate quantification, and the increasing number of data-analysis strategies that are being developed, standards are clearly needed. Metabolomics (like transcriptomics and proteomics) especially needs good databases to store metabolite data and the associated metadata (data about the data). Two current approaches to standardization highlighted at the meeting are the Architecture for Metabolomics (ArMet), the data model for plant metabolomics developed at the University of Aberystwyth, UK [http://www.armet.org], and the Standard Metabolic Reporting Structure (SMRS) [http://www.smrsgroup.org], which is being developed by a consortium of universities and pharmaceutical and industrial companies together with the European Bioinformatics Institute and the UK Medical Research Council.

Many new developments were presented at this year's meeting, and given the great excitement in this blossoming field, 'Metabolomics 2006', to be held in Boston, should be an even more interesting trip.