Guest Editorial

Metabolomics—A New Exciting Field within the "omics" Sciences

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Metabolomics is an emerging field in analytical biochemistry and can be regarded as the end point of the "omics" cascade. Whereas genomics deals with the analysis of the complete genome in order to understand the function of single genes, the majority of functional genomics studies are currently based on the analysis of gene expression (transcriptomics) and comprehensive protein analysis (proteomics). As we are amassing knowledge of the genome, the transcriptome, and the proteome, we have largely forgotten the metabolome. However, changes in the metabolome are the ultimate answer of an organism to genetic alterations, disease, or environmental influences. The metabolome is therefore most predictive of phenotype (Fiehn 2002; Weckwerth 2003). Consequently, the comprehensive and quantitative study of metabolites, or metabolomics, is a desirable tool for either diagnosing disease or studying the effects of toxicants on phenotype.

One of course wonders why metabolomics has lagged behind other "omics" technologies. Possibly this is because the number of metabolites varies dramatically based on how they are counted. Investigators also debate about what compounds are considered metabolites; for example, should vitamins or smaller peptides be included? According to a simple and widely used definition, a metabolite is any substance involved in metabolism either as a product of metabolism or necessary for metabolism. In any case 3,000 major metabolites seem a reasonable number. If we attempt a global and quantitative evaluation, the technology involved is daunting because the physical properties of the compounds are so divergent and they vary dramatically in concentration. Moreover, the metabolome is a dynamic system subjected to significant environmental influences, for example, temporal or dietary.

It is difficult to envision a single platform being developed in the near future that is able to analyze quantitatively all metabolites simultaneously. Thus with all metabolites as our goal, the technological hurdle seems to be the limiting step. At the other extreme, metabolomics can be seen as metabolite profiling or "just" analytical chemistry. So it is nothing new, simply multi-analyte chemistry that biochemists have been doing for decades. Of course metabolomics is simultaneously both and neither of these. Although an "omics" or global view of metabolism is a goal, by no means is universal coverage of all metabolites required for tremendous biological insight. Also whether we work on complete coverage of a single metabolic pathway or on a more global approach to examine multiple metabolites, such multi-analyte analysis is by no means trivial. Nevertheless, successful implementation of metabolomics requires analytical instrumentation that offers high throughput, resolution, reproducibility, and sensitivity, and only an assembly of different analytical platforms will currently provide maximum coverage of the metabolome. To date, metabolomics-type studies rely primarily on nuclear magnetic resonance (NMR) or mass spectrometry coupled to chromatography.

Currently, two complementary approaches are used for metabolomic investigations. In one approach—metabolic profiling—quantitative analytical methods are developed for metabolites in a pathway or for a class of compounds. This approach produces independent information that can be interpreted in terms of known biochemical pathways and physiological interactions. These data represent an independent legacy database since they are quantitative. The disadvantage is that the system is not a universal or "omics" approach. However, the tremendous advances in technology over the past years allow the constant expansion of the number of analytes quantified simultaneously. Technologically, we are at a point where it is often as simple to measure many compounds as to measure one. If we take one step further and assemble a suite of quantitative methods analyzing key metabolites from different biochemical pathways, we can transform metabolic profiling into metabolomics.

The second approach is metabolic fingerprinting. In such metabolomic investigations, the intention is not to identify each observed compound but to compare patterns or fingerprints of metabolites that change in response to disease or toxin exposure. Comparison of fingerprints, often NMR or mass spectra or chromatograms, is performed using statistical tools such as hierarchical cluster analysis or principal component analysis. If these types of analyse results in sample segregation into unique metabolic clusters, further efforts can be made to elucidate the discriminating compounds and subsequently to evaluate these monocytes as potential biomarkers. Being semiquantitative and simultaneously applicable to a wide range of metabolites—this is a true "omics" approach. Such methods are attractive, as they allow investigators to cast a wide net both generating and testing hypotheses. However, the nature of the data makes the observations instrument/platform dependent. The implementation of NMR-based metabolic fingerprinting has marked the beginning of a metabolomics approach as a tool in biochemistry and has proven to be a powerful technique (Nicholson et al. 2002). However, it will only detect high abundance metabolites. Complementary to NMR, mass spectrometry–based tools will provide coverage for metabolic fingerprinting in a lower concentration range, and their use is increasing steadily (Plumb et al. 2003).

The combination of metabolic profiling and fingerprinting will lead to the realization of metabolomics. In one approach, changes in fingerprints correlating to metabolite profiles will be linked to a physiological state, without exact knowledge of fingerprint components. In another approach, discriminating compounds identified in fingerprints will become the focus for quantitative metabolite analyses. Therefore, metabolomics will contribute to our biological understanding both in a mechanistic as well as a predictive manner. However, it could also assist us in improving human health and may be among the first of the "omics" technologies to reach the clinic. Through multiple metabolomics projects, a powerful list of likely markers of variations in health can evolve (Watkins and German 2002). Analyzing this set of biomarkers in a single high throughput assay will provide the clinician with a powerful diagnostic tool.

In genomics and transcriptomics we saw economies of scale as institutional support developed generating infrastructure behind the technologies. Similar support will be necessary to advance metabolomics. For example, a centralized effort to provide isotopic-labeled standards for a wide range of metabolites would tremendously accelerate work in metabolomics as would the development of an integrated pathway map to aid in data interpretation.

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Such a map would introduce us also to the next level of measuring flux through pathways.

Although metabolomics is still in an early evolutionary stage, we can expect to see exciting new developments in the near future. As more quantitative metabolomic databases evolve, we can integrate them with data sets from the other "omics" technologies to enhance the data value and provide greater biological insight than any one "omics" technique alone can offer.

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