

MEETING REPORT

Moving metabolomics from a data-driven science to an integrative systems science

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Abstract

A report on the 7th annual Metabomeeting of the Metabolic Profiling Forum, University of Manchester, Manchester, UK, 25-27 September 2012.

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Introduction

Metabolomics was first recognized as an independent field of scientific research about 10 years ago. The science has since rapidly evolved, with many significant publications in the fields of microbiology, drug efficacy, toxicology, biomedicine, nutrition, ecology, horticulture, and agriculture. Metabolomics is now considered an essential tool in understanding biological function at a systems level, but it continues to face new and challenging obstacles. Here we report on some of the medical highlights of the 2012 Metabolic Profiling Forum's Metabomeeting, in which many of these issues were addressed.

Challenges and strategies

Metabolomics: from an endpoint to systems science

Metabolomics is primarily a data-driven, hypothesis generating science; however, so far most published research has been proof of principle, relying on complex statistical models as the endpoint of a given study. Often conclusions simply state the future 'potential' of metabolomics platforms. The major theme of this year's Metabomeeting was the need to begin using metabolomics as a foundation on which to truly contribute to the wider scientific knowledge base. The importance of this shift was the focus of the plenary lecture by Robert Hall (Plant Research International, Netherlands). The quote by the

French philosopher and mathematician Henri Poincaré presented at the start of Hall's lecture set the tone for the whole meeting: "Science is facts; just as houses are made of stones, so is science made of facts; but a pile of stones is not a house and a collection of facts is not necessarily science."

Several speakers further developed the topic of appropriate biological context and the necessary progression towards integrative systems science. Ian Wilson (Imperial College London, UK) discussed the dangers of presenting molecular biomarkers of disease without thorough validation, both experimental and theoretical. He described how using systems-biology-based kinetic models, integrating metabolomic and enzyme kinetic data, helped clarify the role of glutathione metabolism in acetaminophen toxicity. Julian Griffin (University of Cambridge, UK) used a similar approach, using agonists of transcriptional factors to identify their role in ameliorating type 2 diabetes. Rene Pool (VU University of Amsterdam, Netherlands) described an integrated and computationally efficient approach for using metabolomics data as phenotypes for genome-wide analysis studies (FaSTLMM), allowing the vast quantities of generated data to be readily interpreted.

Spatial resolution and sensitivity

Because of unavoidable detection limits, current metabolomics measurement techniques cannot be applied to single cells or single subcellular compartments; researchers must base their findings on the metabolic profiles of whole tissue sections or biofluids such as serum, urine, or cerebrospinal fluid. The need for improving spatial resolution and developing more sensitive instrumental techniques was addressed several times throughout the conference. Using different colors of cell-type-specific fluorescent proteins and fluorescence activated cell sorting, Aharoni Asaph (Weizmann Institute of Science, Israel) was able to explore the metabolotypes of specific *Arabidopsis* root cell types. Although far from trivial, application of this approach to mammalian model systems would offer new insights into the specific metabolic roles of individual cell types within their respective healthy or diseased tissue.

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To properly use such a strategy, analysis of minute samples must also be possible. Current analytical techniques are too insensitive to provide metabolomic analysis of samples as small as a few microliters or nanoliters. The inability to analyze microscopic intact tissue biopsies remains a major obstacle in effectively using personalized medicine strategies. Alan Wong (CEA Sarclay, France) has addressed this need by developing a technique for high-resolution magic angle spinning (MAS) nuclear magnetic resonance spectroscopy of nanoliter sample sizes. Using a solenoid micro-coil that can be wirelessly excited by and detected with a conventional MAS probe, Wong was able improve instrument sensitivity 17-fold. This could, theoretically, enable the researcher to quantify a much lower abundance of metabolites, such as that found in limited-volume samples in biofluids or tissue samples from animal models. Nick Lockyer (University of Manchester, UK) discussed the ability to obtain chemically derived two-dimensional and three-dimensional images of cells and tissues using secondary ion mass spectrometry (SIMS); while still a developing technique, this provides the spatial resolution necessary to move towards subcellular metabolomics.

Data analysis and metabolite identification

This year's discussions regarding the computational aspects of metabolomic research shifted away from the usual topic of novel statistical methods, and instead focused on the pressing need for improvements in metabolite identification and database curation. Rainer Breitling (University of Glasgow, UK) described recent developments with *mzMatch*, a flexible command-line tool for the processing, filtering, and annotation of mass spectrometry data. Carsten Kuhl (Leibniz Institute of Plant Biochemistry, Germany) described an alternative approach to feature detection and annotation based on the popular *XCMS* software package. This new set of tools, called *CAMERA*, allows rapid high-throughput analysis of liquid chromatography mass spectrometry (LC-MS) data, automating many feature-grouping and annotation tasks that until recently required manual inspection.

Publicly available data repositories are essential if metabolomics is to gain credibility within the larger scientific community. Reza Salek (EBI, UK) presented an overview of one such repository, *MetaboLights*, supported by the European Molecular Biology Laboratory (EMBL). *MetaboLights* is a database for metabolomics experiments and information derived from them. The database is cross-species, cross-technique and covers metabolite structures and their reference spectra as well as their biological roles, locations and concentrations, and experimental data from metabolic experiments.

Scientific advances using metabolomics as a tool

Food and nutrition

Plant products are integral in our diets and thus human health. Benzoxazinoids are secondary plant metabolites known to have a role in host immune response that have recently been found in whole grain and baking products. Relationships such as these have prompted the food industry to respond with claims of health benefits to increase product sales. However, our bodies do not process every plant product in the same way. Khem Bahadur Adhikari (Aarhus University, Denmark) measured benzoxazinoid derivatives using a pig model exposed to different cereals. He found that the fecal metabolome provided information on digestibility of each cereal, whereas plasma and urine metabolomes were indicative of metabolism and excretion of these products. This study highlights the need for greater exploration of how foods are incorporated into the body in addition to their own composition.

The quest for establishing relationships between food and health continues at the consumer level; exposure level and frequency are two critical factors dictating this relationship. However, it is extremely difficult to determine causal relationships between food consumption and health effects. As Amanda Lloyd (Aberystwyth University, UK) highlighted, conventional methods of determining dietary exposure rely too heavily on questionnaires that are subject to participant interpretation and are therefore subject to error. Lloyd, with the rest of John Draper's group, discovered that the consumption frequency of several food groups could be determined from urine composition. Continuation of this study will help define habitual diet patterns so that their effect on health can be more effectively explored.

Quality assurance is another important aspect in the food industry. Although spoilage of certain foods leads to nothing more than an unpleasant taste, that of others can cause serious illness. As George Nychas (Agricultural University of Athens, Greece) emphasized, relying on molecular methods to detect microbial presence in food is a time-consuming task that requires a high level of expertise. Using gas chromatography (GC)-MS and high performance liquid chromatography (HPLC), Nychas' group was able to determine freshness of beef and table olives with a correct classification rate of over 80%.

Human disease and drug development

Discussions of disease at the meeting focused largely on lipid metabolism. Insulin resistance and type II diabetes have become global health concerns. Julian Griffin (University of Cambridge, UK) discussed two rare inherited disorders causing insulin resistance, lipodystrophy and insulin receptoropathies, and revealed the critical role of lipid metabolism and the body's response to nutrient

availability in their differential pathophysiology. Stacey Reinke (University of Alberta, Canada), in her award-winning oral presentation, highlighted that perinatal hypoxic-ischemic brain injury is associated with systemic inability to use lipid stores for energy production and generation of neuro-protective ketones. Andrew Southam (University of Birmingham, UK) explored the adaptive ability of cancer cells to protect against oxidative cell death by altering lipid composition. He applied this knowledge to investigating the mechanisms of individual and combined anti-cancer treatment.

Conclusion

Metabolomics has come of age, although there are still many challenges ahead. The bottleneck of metabolite identification is still an imposing factor stifling current

research, but computational and technological platforms are both developing at an incredible speed. The pressing need is now to consider the biological context of a given study and integrate metabolomics into the bigger scientific picture. It was clear from this meeting that the combination of metabolomics with other systems-level technologies will provide valuable insight into biological mechanisms and fuel future research in this field for many years to come.

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