Genome Medicine

EDITORIAL

Metabolomics: the final frontier?

Timothy D Veenstra*

The connection between genomics, proteomics and metabolomics is evident in even the most simplistic of scientific models. Genes give rise to mRNA. Proteins are translated from mRNA and then proceed to carry out a myriad of functions within the cell, including the metabolism of small molecules such as glucose and adenosine triphosphate. Not that many years ago, scientists used to study the 'big 4' biomolecules under the guise of genes, transcripts, protein and metabolites. The last decade of biomedical research, however, has been witness to the growth of the 'omics' industries. Genomics, transcriptomics and proteomics have become core technologies within almost every major academic or industrial research program around the world. What was missing was the final piece of the omics puzzle: metabolomics.

Mass spectrometry or nuclear magnetic resonance?

From a technology perspective, metabolomics has come along at precisely the right time. The two major technologies used to gather metabolomics data, mass spectrometry (MS) and nuclear magnetic resonance (NMR) spectroscopy, have both reached fantastic heights of data gathering capability [1,2]. Comparatively speaking, however, MS and NMR spectroscopy have their own specific advantages and disadvantages when conducting metabolomic studies. The main advantage of MS is sensitivity, as state-of-the-art mass spectrometers can detect analytes routinely in the femtomolar to attomolar range. Coupling MS with liquid chromatography (LC) or gas chromatography (GC) enables the measurement of hundreds of individual species within a single sample. The combination of mass accuracy and real-time tandem MS available with many mass spectrometers, along with increasingly comprehensive databases, is making the identification of these metabolites more routine. One of the major weaknesses of MS in metabolomics is quantification. The MS signal intensity of any compound is affected by the type of sample preparation used and its molecular environment. Adding known amounts of internal isotope-labeled standards enables accurate quantification for specific molecules; however, this strategy is impractical for purely discovery-driven metabolomics research. Most studies rely on comparing peak area or intensity to locate differences in the relative abundance of specific metabolites between samples. However, these measurements can suffer from a lack of accuracy and precision.

The major weaknesses of MS are the major strengths of NMR spectroscopy. The peak area of a compound in the NMR spectrum is directly related to the concentration of specific nuclei (for example, ^{1}H, ^{13}C), making quantification of compounds in a complex mixture very precise. A metabolite detected as being more abundant in a specific sample can be identified either through the resonance positions of its nuclei in the NMR spectrum, or through the application of various pulse-sequences such as total correlation spectroscopy, heteronuclear single quantum coherence and heteronuclear multiple bond correlation. Another underappreciated character of NMR spectroscopy is its versatility for analyzing metabolites in the liquid state (serum, urine and so on), in intact tissues (for example, tumors) or *in vivo*. Unfortunately, sensitivity, which is the major strength of MS, is the major weakness of NMR spectroscopy. Although cryogenically cooled probe technology, higher field-strength superconducting magnets [3] and miniaturized radiofrequency coils [4] have increased sensitivity, NMR spectroscopy is still orders of magnitude less sensitive than MS.

While metabolomics is less mature than genomics and proteomics, it is already making a major impact in a wide variety of scientific areas, including newborn screening, toxicology, drug discovery, food safety and biomarker discovery (Figure 1). As with genomics and proteomics, most of the pressure will be on metabolomics to find biomarkers of diseases such as cancer. Investigators have already shown the potential promise of metabolomics in this area. For example, Sreekumar *et al.* [5] used LC-MS and GC-MS to profile 42 tissue, 110 urine and 110 plasma samples from patients affected with benign prostate disease, clinically localized prostate disease and metastatic disease. Not only were they able to distinguish these three conditions based on the NMR data, but they found that a specific metabolite, sarcosine, was highly

*Correspondence: veenstrat@mail.nih.gov
Laboratory of Proteomics and Analytical Technologies, SAIC-Frederick, Inc., Frederick National Laboratory and Research Center, Frederick, MD 21702, USA