The Human Serum Metabolome

Introduction

While it is relatively routine in genomics/transcriptomics and proteomics studies to identify and quantify 100s of genes or proteins at a time, the same cannot be said of most metabolomics efforts. In an effort to further enhance the use of quantitative metabolomics, we (and others) have started to systematically determine the detectable metabolite composition of clinically important bodily fluids and tissue types. In order to facilitate future research into blood chemistry and blood metabolomics, it is crucial to establish a comprehensive, electronically accessible database of the detectable metabolites in human blood or human serum. Herein we present just such a database describing the detectable metabolites (including their concentrations and disease associations) that can be found in human serum.

Objectives

- Compare various metabolomic technologies, estimate their coverage and breadth and suitability for studying blood serum
- Obtain values from literature
- Validate literature values
- Identify and expand the coverage of what is known in the serum metabolome and disease associations
- Text mining/Bibliomics

With respect to the literature survey, more than 1000 references were studied, producing a list of 1087 metabolites purported to be present in human serum. Of the latest metabolites, 1027 of them have at least one reported normal concentration value and 479 have at least one concentration range. Comprehensive tables containing the compounds, spectra, protocols and links to disease associations that were revealed or identified from these combined experimental and literature mining efforts are presented, which are also freely available at http://www.serummetabolome.ca.

Text mining/Bibliomics

From 4 methods Combining the metabolites identified in both polar extracts and lipid extracts, 70 metabolites were identified (Table 2).

NMR Spectroscopy

In total, 63 samples were analyzed: 15 from healthy subjects and 49 from heart transplant patients. 1H-NMR spectra were collected for each sample using the Inova pulse sequence on a 500 MHz Inova Varian spectrometer. The spectra were processed using Chenomx NMR suite software v. 6.0 (Figure 1). Assigned compounds were confirmed with spiking analysis. At least 90% of the area in each spectrum was accounted for.

37 metabolites were identified in healthy subjects and 44 in heart transplant patients. Serum pool together with 30 metabolites were found significantly different between the two groups (p-value < 0.05) (Table 1). From the 37 compounds identified in the control serum group, 32 had corresponding concentration values in the literature, from which 12 had comparable concentrations, 12 significantly lower and 3 significantly higher concentrations compared with those determined by our group.

LC/ESI-MS/MS

Four human plasma sample replicates were extracted by Solid Phase Extraction (SPE) and analyzed by LC-ESI-MS/MS for a list of over 2000 polar compounds. Of the 37 metabolites identified in the control serum group, 33 had corresponding concentration values in the literature, from which 12 had comparable concentrations, 12 significantly lower and 3 significantly higher concentrations compared with those determined by our group.

Table 1. List of polar and lipid compounds identified by NMR

Table 2. List of polar and lipid compounds identified by LC-ESI-MS/MS

Conclusions

Global metabolomic profiling methods can routinely detect about 3300 different compounds in serum. In total, an average of 32 compounds were detected and quantified with NMR spectroscopy, 78 compounds with GC-MS, 84 oxylipid and 103 compounds with LC/ESI-MS/MS, 25 CEs, 30 LPYCs and 27 FFAs with TLC/GC-FID. This method was able to detect and quantify about 70 compounds, LC-ESI-MS/MS techniques were able to quantify 84 oxylipid mediators, whereas with LC-ESI-MS/MS more than 3100 lipids were quantified. Comprehensive, web-accessible tables containing the compounds, concentrations, spectra, protocols and links to disease associations that were revealed or identified from these combined experimental and literature mining efforts are presented, which are also freely available at http://www.serummetabolome.ca.