Application of the accurate mass and time tag approach in lipidomics studies of type 1 diabetes mellitus

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Overview

- Samples from the Diabetes Autoantibody Standardization Program (DASP) investigated
- Lipid extraction in conjunction with LC-MS-based lipidomics applied
- Detected lipids matched to an accurate mass and time (AMT) tag database in order to identify molecular species
- Identified lipid abundances compared using a t-test and visualized in principal components analyses (PCA) plots to identify candidate biomarkers
- Additional lipids not matched to the database were also compared using t-test and PCA to select biomarkers for future structural elucidation

Introduction

Both glucose and lipid metabolism are altered during type 1 diabetes mellitus. While some classes of lipids have been reported to be perturbed during this disease, information regarding individual lipids is scant. In this study, we utilized capillary liquid chromatography (LC) coupled with Fourier transform ion cyclotron resonance (FTICR) mass spectrometry (MS) to analyze plasma and serum lipids from control individuals and patients recently diagnosed with type 1 diabetes.

We matched features to an in-house lipid accurate mass and time (AMT) tag database. These matched features were selected for comparative analysis using a t-test and principal component analysis (PCA) to identify candidate biomarkers of type 1 diabetes. Additional potential lipid biomarkers were selected during another comparative data analysis based on confidence metrics (‘complete data’) and statistical testing. These comparisons were made to explore the lipidome and select additional biomarkers of type 1 diabetes.

Methods

- Plasma and serum lipids were extracted in lipipate using chloroform/methanol and the chloroform fraction was analyzed by capillary LC-FTICR MS.
- MS-MS measurements were within 100 - 1,000 m/z. Reduction of chemical noise by intensity thresholding during feature identification was made.
- Raw MS spectra were declustered to give the monoisotopic mass, charge state, and intensity of the major peaks in each spectrum.
- Features from the declustered spectra were assigned to an observed monoisotopic mass and normalized elution time (NET).
- The data were chromatographically aligned and matched to a previously established lipid AMT tag database using tolerances of ± 0.12 ppm and ±0.003 NET.
- Evaluation of matches to the database with the mass and NET tolerance parameters produced a 1% false discovery rate based on a uniform addition of 11 Da mass shift to the database.
- Matched features (n=60) were selected for subsequent comparative data analysis using t-test (P<0.05) and principal components analysis (PCA) to identify candidate biomarkers of type 1 diabetes.
- A parallel examination of all reproducible features (n=60) that were significantly different (P<0.05) between control and patient samples was made to explore the plasma lipids and select additional biomarkers of disease.

Results

- Features reproducibly observed were tabulated in Table 1.
- Significant features at P<0.001 for Principal Component 1 and Principal Component 2 are shown in Figure 2 and Figure 3, respectively.
- Features matched to the database were tabulated in Table 2.
- Figure 4 shows the loadings plot of significant matched features with differences in principal component scores for control (light blue) and type 1 diabetes (red).
- Table 2. Lipid identities and assignments for significantly different features (P<0.05, P<0.01) matched to the database. Relative higher abundance is indicated by control (C) or patient (P).
- Additional analyses of all features indicated that 71 unidentified lipids were significantly different (P <0.05) in patient versus control samples.
- Significant perturbations of the plasma lipidome in type 1 individuals were revealed using t-test and PCA approaches.
- Three identified GPCoH and T SM were found to be abundant in patient samples relative to control samples, consistent with other report6.
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