Biomarker Discovery in Cerebrospinal Fluid for Schizophrenia and Antipsychotic Drug Treatment-Induced Weight Gain.

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Introduction

Schizophrenia is a complex neuropsychiatric disorder with both behavioral and cognitive alterations and an onset in early adulthood. However, diagnosis still relies on interview-based processes and no useful biomarker has been found for clinical application. Cerebrospinal fluid (CSF) is a promising source for detecting neurological disease-related biomolecular alterations. Here, we performed a protein marker discovery study on CSF samples from schizophrenic and healthy subjects using a label-free proteomics approach previously used for finding Central Nervous System lymphoma biomarkers (1-3).

Methods

15 healthy individuals and 15 schizophrenic patients (age and gender matched) were recruited for this study. As part of an earlier technical study, a second CSF sample obtained one month later was analyzed concurrently and provided an extra measure or verification of observed changes. CSF samples from 15 healthy controls (n=15) and the two times visit of 15 schizophrenic patients each (n=15x2) were subjected to MARS-14 depletion of abundant proteins and digested with trypsin. Sample analysis was performed using 2D-LC-MS in combination with Strong Cation Exchange Chromatography and a Thermo QExactive LC-MS system. Statistical and pathway analyses were utilized to investigate biological signatures of the disease.

Results

Total 9829 unique peptides are sequenced and 1239 proteins identified in CSF. Proteins are differentially expressed. Here, we performed a protein marker discovery study on CSF samples from schizophrenic and healthy subjects using a label-free proteomics approach previously used for finding Central Nervous System lymphoma biomarkers (1-3).

Diseases or Functions Annotation p-Value Activation z-score # Proteins

Nervous System Development and Function

Development of central nervous system 2.32E-06 0.612 23
Synaptogenesis 9.12E-05 -1.491 9
Nerve growth 4.91E-11 -1.066 17
Genetic transmission 4.09E-06 -1.002 16
Neurogenesis 1.95E-13 -1.218 30

Up-regulated proteins related to Inflammation

Diseases or Functions Annotation p-Value Activation z-score # Proteins

Inflammatory Response

Activation of myeloid cells 1.19E-03 2.01 10
Adhesion of phagocytes 7.74E-04 1.664 7
Complement activation 2.66E-13 1.96 11
Activation of lymphocytes 2.11E-03 1.709 18
Phagocytosis of cells 4.30E-05 0.382 12
Immune response of T lymphocytes 1.53E-03 -1.067 6

Figure 2. Heatmap of differentially expressed proteins in Schizophrenic patients vs. healthy individuals. Threshold: fold change 1.25, p & q value <0.01

Figure 3. Averaged z-score (average of all peptide z-scores per cohort for four different Neuronal associated example proteins (# peptides per protein is reported above)

Figure 4. Averaged z-score (average of all peptide z-scores per cohort for four example proteins related to inflammation (# peptides per protein is reported above)

Figure 5. Heatmap of 63 differentially expressed proteins between anti-psychotic drug treat patients with and without weight gain

Summary

- Relative intensities of detected proteins in the disease cohort were the same between the two visits a month apart.
- Down-regulated neuronal-associated proteins were observed in subjects with Schizophrenia.
- Inflammation-related proteins were up in Schizophrenia.
- Protein expression correlated with antipsychotic treatment leading to significant weight gain, a significant issue in therapy.
- An in-depth investigation of proteomic changes in CSF associated with Schizophrenia was obtained.

The candidate biomarkers described here require verification and may facilitate effective diagnostics and utility in clinical trials for monitoring efficacy; biomarkers indicating adverse effects such as weight gain sue to antipsychotic agent therapy may be used for monitoring improved therapies.

References

1. Roy et al., JCO 2008; 26(1):96-105
2. Wang et al., Analytical chemistry 2003; 75(18):4818-26

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