Investigation of the human blood plasma depletome of schizophrenia patients in the search for more effective antipsychotic treatments: establishing the methods

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Abstract

Schizophrenia is a chronic disorder whose molecular mechanisms are still to be unraveled. Although diagnostic criteria are well established, the treatment choice is still made by trial and error. About one third of schizophrenia patients do not respond properly to antipsychotic treatment. Therefore, it is necessary to search for biomarkers that predict a successful response to medication. And this answer may be in the human blood plasma proteome. High-abundant proteins are depleted by affinity chromatography from the blood plasma prior to large scale proteome analysis in order to obtain the low-abundance fraction, where the main biomarkers are expected to be found. But this process may remove potential biomarkers inadvertently. Thus, the analysis of the high-abundant fraction (the depletome) is certainly a relevant question in the quest for biomarkers towards effective treatments to schizophrenia. Here we show our first results and optimization on studying the human blood plasma depletome.

Key words: Schizophrenia, biomarkers, proteomics.

Introduction

Schizophrenia (SCZ) is a chronic disorder that involves changing brain macro- and microconnectivity. It affects 1% of the world population and its symptoms normally appear in young adults (1). SCZ patients present positive symptoms, such as delusions and hallucinations, negative symptoms, such as social withdrawal and loss of volition, and also cognitive symptoms.

As an incurable disorder, the main way of managing schizophrenia is antipsychotic medication. Antipsychotics are classified in two classes: conventional or first-generation antipsychotics (FGA), and atypical or second-generation antipsychotics (SGA). Both classes act as dopamine D2 receptor blockers. FGA present greater effect on positive symptoms, but they may cause extrapyramidal or tardive dyskinesia side effects(2). Some of the SGA may act on negative symptoms and present less extrapyramidal side-effects, even though they have significant metabolic adverse effects(3,4).

Several studies suggest that blood plasma displays molecular indicators (biomarkers) of neurological changes. As these biomarkers can be proteins, it is reasonable to investigate the proteome of SCZ blood plasma while searching for them(5).

The plasma proteome may present over 10 thousand different proteins, with concentrations around 12 orders of magnitude(6). The greatest diversity of proteins is found in low-abundance, while few proteins represent the high-abundant fraction. This is normally separated by the low-abundant fraction prior to proteome analysis by affinity chromatography, in order to facilitate the identification of the latter. The high-abundant fraction, or the "depletome"(7) may be analyzed by shotgun mass spectrometry aiming to reveal biomarkers at very low detection levels that were inadvertently removed with the proteins of high-abundance.

The blood plasma depletome is a source of potential biomarkers, which may be able indicate the effectiveness of antipsychotic treatment to SCZ patients prior to medication. Also, these proteins may help to elucidate the mechanisms of the disease.

Here we show our first results and optimization on studying the human blood plasma depletome.

Results and Discussion

Blood plasma samples of healthy volunteers were used in this study towards the standardization of sample preparation methods. The depletome was obtained by immunoaffinity chromatography able to deplete 14 abundant plasma proteins (MARS column Hu14, Agilent). After sample preparation, the depletome is analyzed by shotgun mass spectrometry. The identification and quantification of proteins are executed by Progenesis software. Finally, systems biology in silico will be performed to correlate identified proteins to their metabolic pathways.

Conclusions

This work did not own conclusions at the time of submission for this congress.

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