



Molecular dysfunction in anterior temporal lobe of patients with schizophrenia reveals linking between energy and signaling pathways

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Abstract

Schizophrenia (SCZ) is a chronic and mental disorder characterized by the presence of positive, negative and cognitive symptoms. Although molecular mechanisms involved in SCZ is still unknown, there is a dysfunction on energy metabolism and cellular signaling. To clarify potential linking between these pathways, we enriched three cellular compartments and carried out bottom up proteomics analysis to find proteins related to pathophysiology of disease.

Key words:

Schizophrenia, Proteomic, Mass Spectrometry

Introduction

Schizophrenia (SCZ) is a chronic and mental disorder that affects more than 21 million people worldwide. Although that illness could be diagnosed by the presence of positive (e.g. hallucinations), negative (e.g. social withdrawal) and/or cognitive symptoms, the molecular mechanisms involved in the brain of these patients are still limited.¹

The Anterior Temporal Lobe (ATL) is an important brain region for auditory and visual processing, language and memory. The dysregulation of mitochondrial and synaptosomal homeostasis in this brain are has been suggested. Therefore, by enriching these cellular compartments and analyzing their proteomes employing bottom up shotgun proteomics could reveal how the energy metabolism is connected to cellular signaling. This will clarify potential mechanisms of the disease and future therapeutic targets.

Results and Discussion

We enriched mitochondria and synaptosomes from the ATL collected postmortem from patients and mentally healthy controls. Next, we carried out the extraction of proteins, which were digested with trypsin. Resultant peptides were submitted to LC-MS/MS analysis. Obtained Spectra were processed by specialized software, which identify and quantify proteins present in the sample.

We found 174 differentially expressed proteins. Out of these, 27 are associated to glycolysis, acid citric cycle and electron transport chain, suggesting decreased energy output and increased oxidative stress. Moreover, several of these proteins affect glutamate metabolism (Figure 1), the major excitatory neurotransmitter of the human brain.

Previous reports have shown the hypofunction of glutamate system in SCZ patients. The hypothesis around these neurotransmitters suggest that cognitive and negative symptoms precede positive symptoms, which are associated to dopaminergic function. Thus, the hypofunction of glutamate might lead to hyperfunction of dopaminergic system and both are responsible for the pathophysiology of schizophrenia.²

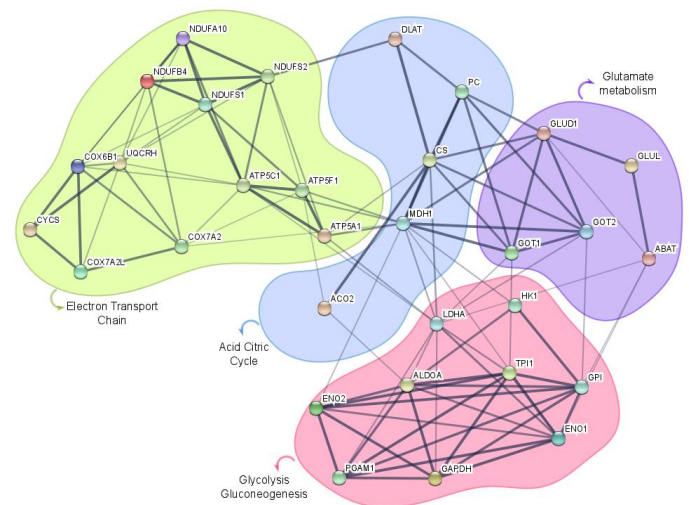


Figure 1. Metabolic proteins found differentially expressed in schizophrenia. <https://string-db.org>

Conclusions

If validated by further experiments, our findings suggest a potential link between two important pathways found dysregulated in schizophrenia. Hence, these results clarify some mechanisms of disease and can help in the improvement of the patients' treatment.

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² Kahn R, Sommer I, Murray R, Meyer-Lindenberg A, Weinberger D, Cannon T et al. Schizophrenia. *Nature Reviews Disease Primers.* 2015;:15067.