

Proteomics Tackling Schizophrenia as a Pathway Disorder

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As a complex combination of genetic, neurodevelopmental, and environmental components, schizophrenia is one of the most difficult human disorders to be understood at the molecular level. The countless combination of biochemical and environmental variants leads to intricate webs of molecular interactions, which are not exclusive to the brain, hampering the identification of not only the causes and consequences of schizophrenia but also the discovery of biomarkers. During the last century of schizophrenia research, trusting the comprehension of this complex disorder in central pieces does not seem the best way. None of the proposed hypotheses such as dopaminergic, glutamatergic, serotonergic, neurodevelopmental theories can be sustained by themselves. But they do make sense when combined. Additionally, it is clear that “a single biomarker for schizophrenia”—as for Alzheimer’s disease, and prostate cancer—it is not going to be revealed.

Revealing which pathways are altered in schizophrenia seems to be the way to solve its molecular understanding and even the quest for biomarkers. Recently, Patrick F. Sullivan¹ has defended this point, exploring how genetic variants functioning together may lead to diseased states, highlighting the polygenic feature of schizophrenia. Several genetic differences of small effect—especially if these are components of the same biochemical pathway—added to environmental factors² can trigger the disorder. But each one of these small differences is not significant to be noted alone, explaining why multiple genetic studies have failed to identify a single gene responsible for schizophrenia. The understanding of schizophrenia does not demand the characterization of individual molecules but their combined interaction. Sullivan additionally suggested other evidences that support schizophrenia as a disease of biochemical pathways, such as the absence of Mendelian forms of schizophrenia and its similarity to

bipolar disorder. The distinction between schizophrenia and bipolar disorder might be just the result of a slightly different tuning of the several molecular interactions.

Assuming schizophrenia a pathway disorder, proteomics is, by definition, one of the suitable approaches for its understanding and for the establishment of biomarker panels. The early definition of “proteome” coined by Wilkins and colleagues³ about 15 years ago explains the utility of proteomics for studying pathway disorders. The advantage of proteomics is to pinpoint which pathways are altered in an ocean of biochemical interactions through the precise identification of protein players using highly sensitive and accurate mass spectrometry. Discovering the involved pathways can lead to a better comprehension of the disorder, and the most consistent protein candidates can be combined using statistics tools in a multidimensional manner for the establishment of biomarker panels.

The differential expression of proteins involved in neuronal transmission, synaptic plasticity, calcium homeostasis, and immune system in schizophrenia patients was observed using proteomic techniques.⁴ One of the most consistent dysfunctions observed is in energy metabolism pathways.⁵ At first these only seem a confirmation of previous findings,⁶ which lack in specificity, since energy metabolism dysfunctions are a trait marker of psychiatric disorders in general. However, energy metabolism is composed of numerous catabolic and anabolic pathways such as glycolysis, gluconeogenesis, and glycogen metabolism; tricarboxylic acid cycle; oxidative phosphorylation; fatty acid oxidation and lipogenesis; amino acid metabolism, urea cycle and nucleotide metabolism; pentose phosphate pathway and several others. Proteomic studies have been pinpointing which specific pathways are differently altered for each disorder and the central regulators of each of the pathways. For instance, while glycolysis seems to be the most affected energetic pathway in schizophrenia⁵, oxidative phosphorylation appears

to be more prominently altered in major depressive disorder.⁷ Proteomic profiling studies have also shown⁸ that oligodendrocyte dysfunction plays a pivotal role in schizophrenia as previously proposed⁹ and consistent with transcriptomic findings. Recently, the clathrin-mediated endocytosis pathway has been hypothesized as a central component of schizophrenia pathobiology, supported also in proteomic findings, which suggests that the clathrin interactome may be a useful target for pharmacological manipulation.¹⁰ Additionally, biomarker studies using blood serum from schizophrenia patients have been carried out using proteomics.¹¹ In this manner, proteomic approaches have provided novel insights into schizophrenia, which otherwise may have remained undiscovered.

There are still proteomic techniques to be explored in schizophrenia research that can enrich the current knowledge. Subproteomes can be thoroughly studied if there is interest in a particular pathway. High throughput mass spectrometry techniques such as selective reaction monitoring (SRM) can be used for the simultaneous quantitative analyses of all enzymes of a given pathway of interest. SRM can also be used as a diagnostic or drug treatment response tool by the measuring panels of biomarkers comprising specific pathways in a multivariate manner.¹² Proteomic studies can also provide information about posttranslational modifications and protein-protein interactions, which provide a useful means for increasing our comprehension of complex disorders. Prognostic studies, medication efficacy, establishment of preclinical models, and patients' stratification can also be aided by proteomics via the identification of molecular phenotypes. Proteomics is therefore a tool to be implemented in combination with others to facilitate more complete understanding and for revealing biomarkers of pathway disorders in schizophrenia.¹

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