Comprehending depression through proteomics

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Even being a severe neuropsychiatric disorder affecting approximately 10% of the population worldwide, the molecular mechanisms underlying depression, unipolar depression, clinical depression or major depressive disorder (MDD) are still to be comprehended (Fava & Kendler, 2000). One of the main challenges is to understand how the multifactorial characteristics of MDD – which come from genetic or metabolic predisposition triggered by environmental factors – are connected to each other. But in order to understand their interaction, it is necessary to characterize each one of these factors.

Key molecular components of MDD such as genetics (Goltzer-Dubner et al. 2010), gene expression (Mehta et al. 2010) and a range of studies in preclinical models (Muller & Holsboer, 2006) have been investigated. But one of the key components of the molecular basis of MDD – the proteome – has just started to be characterized in human tissues. Proteome was defined around 15 years ago as the total set of expressed proteins by a cell, tissue or organism at a given time under a determined condition (Wilkins et al. 1996). This definition led to the science currently known as proteomics that also included the study of protein–protein interactions and post-translational modifications. The identification of sets of differentially expressed proteins or even the differential post-translational modifications of proteins while studying samples from MDD patients may lead to two main outcomes: (1) revealing proteins, and consequently metabolites and biochemical pathways which may shed light on the comprehension of pathological states; (2) revealing biomarker candidates with potential for therapeutic applications (Martins-de-Souza et al. 2010). Non-hypothesis-driven proteomic applications offer different insights of MDD by complementing those provided by the standard targeted methodologies.

Regarding the molecular comprehension of MDD, post-mortem dorsolateral prefrontal cortex from 24 MDD patients and 12 matched controls were analysed using label-free proteomics. Distinct proteome fingerprints between MDD and controls associated with energy metabolism and synaptic function were observed. Additionally, differential proteome profiles in MDD with and without psychosis were assessed showing a marked overlap to proteome changes seen in schizophrenia brains (Martins-de-Souza et al. 2012a). Complementarily, a shotgun proteomics approach has been used also to identify differences in the phosphorylation of brain proteins compared to controls. The majority of phosphorylation differences were associated with synaptic transmission and cellular architecture (Martins-de-Souza et al. 2012b). Other studies in brain tissue from MDD patients were performed previously using anterior cingulate cortex (ACC) and frontal cortex (FC) (Beasley et al. 2006; Johnston-Wilson et al. 2000). Both showed the altered expression of carbonic anhydrase (CA2) and Aldolase C (ALDOC), suggesting effects on energy metabolism. Additionally, dihydropyrimidinase-related protein-2 (DPYSL2) was also found common to both studies, but down-regulated in FC and up-regulated in ACC. However, these studies focused on schizophrenia using MDD samples as controls for specificity.

Considering the lack of biochemical markers for MDD that could aid, for instance in patient stratification, the proteome of the cerebrospinal fluid (CSF) from 12 MDD patients and 12 controls were evaluated recently (Ditzen et al. 2012). Using traditional proteomic methodologies such as two-dimensional gel electrophoresis followed by matrix-assisted laser desorption ionization–time-of-flight–mass spectrometry (MALDI-TOF-MS), 11 proteins were observed as differentially expressed including...
protein players in neuroprotection, neurodevelopment and sleep regulation.

In their recent publication, Xu and colleagues present a proteome analysis of the plasma from 21 first-onset drug-naive MDD patients which were compared to 21 controls using shotgun proteomics for protein identification and isobaric tags for relative and absolute quantitation (iTRAQ) for protein quantitation (Xu et al. 2012). The study focuses on the understanding of MDD as a systemic disorder, but also mentions the biomarker potential of these candidates. By using this proteomic hypothesis-free approach and a further validation by Western blot and enzyme-linked immunosorbent assay (ELISA), Xu et al. identified 94 proteins and found nine of those differentially expressed in MDD patients. These are mostly involved with lipid metabolism and the immune system and authors suggest that these are processes that might be involved in the early stages of MDD pathophysiology.

Proteomic studies mentioned here have indeed provided understanding of the molecular aspects of MDD, exploring not only the role of the proteins, but also the role of biochemical pathways and related metabolites. However, only the report from Ditzen et al. (2012) in MDD CSF explored reasonably the differentially expressed proteins as biomarkers candidates for MDD. This aspect of proteomic studies is still open to exploration in order to reveal proteins that can be useful not only in diagnosis, but in patient stratification in accordance with the different types of MDD (i.e. atypical depression and psychotic depression), prognosis, treatment monitoring and response, and potential drug targets.

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Statement of Interest

None.

References


