Deregulated exosomal microRNA as a biomarker in bipolar disorder

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Research question and background

Bipolar disorder (BD) is the 6th leading cause of disability worldwide and the most expensive mental health care diagnosis, while direct and indirect annual costs for 1% of Americans living with schizophrenia (SZ) are estimated at US$ 23 billion. The lack of biomarkers needed to increase diagnostic accuracy, help monitor, and better treat these costly and common chronic mental disorders is the *critical barrier* towards their biological definitions and towards the reduction of the humanistic and economic burden carried by the afflicted patients and their families. Central nervous system neurons and glia release exosomes that modify functions of recipient cells by shuttling microRNAs (miRs) capable of altering the recipient cell proteome. *Our central hypothesis* is that miRs packaged into exosomes that are found in serum and CSF represent a read-out of specific alterations in transcriptional regulation of the proteome in SZ and BD. This hypothesis is rooted in our R21 MH086079- funded published study that identified two miRs with significantly altered expression in exosomes extracted from postmortem prefrontal cortex of patients diagnosed with SZ (miR-497) and BD (miR-29c). *The objective of this proposal* is to employ Next Generation Sequencing (small RNA-Seq) to identify exosomal miRomes in serum and CSF samples of SZ and BD as well as major depressive disorder (MDD) patients and non-psychiatric controls. MDD samples will be analyzed because of the clinical and pathological overlap between MDD and BD and because of comorbid depressive symptoms in SZ patients. By obtaining exosomal miRomes in serum and CSF of psychiatric patients and controls, *we expect to* uncover exosomal miRome signatures as biomarkers for each psychopathology. To generate pathogenesis-relevant hypotheses for evaluation beyond this proposal, we will also determine the expression of top differentially expressed exosomal miRs in SZ and BD serum and CSF samples in neurons and glia of postmortem cortices.

Methods and tissues used

Serum and CSF exosomal miR biomarkers expression will be determined in neurons and glia that are obtained via laser-microdissection from frozen cortices (cingulate, BA24, and prefrontal, BA9) of patients diagnosed with bipolar disorder or schizophrenia (respectively) and controls.

Results (unpublished) and conclusion

We micro-dissected 2,000 pyramidal neurons and 2,000 glial cells, oligodendrocytes and astrocytes, from BA24 of three control cases and three familial BD cases. We performed qPCR using cDNA made from the small RNA extracted from the captured material. Our qPCR analysis suggests that the glia population might be responsible for the increase in BA24 exosomal miR-149 expression in BD cases, consistent with miR-149 negative regulation of cell proliferation.