Exosomal and cell-class specific miRNA-profiles in bipolar disorder

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Research question and background
Bipolar Disorder (BD) is a costly, common, and highly polygenic disease with marked clinical heterogeneity and phenotypic and genetic overlap with other mental diseases. Early identification of individuals who will become BD or major depressive disorder (MDD) patients with bipolar features will have therapeutic consequences and could contribute to better treatment and prognosis. However, BD biomarkers do not exist in clinical practice.

We propose to test the hypothesis that microRNA (miR) content in exosomes, microvesicles that are excreted by neurons and glia and present in cerebrospinal fluid (CSF) as well as in plasma, may serve as biomarker distinguishing BD patients from healthy individuals. Our recent studies of postmortem prefrontal (BA9) and anterior cingulate (BA24) cortex exosomal miRNA yielded to putative miR candidates, miR-29c and miR-149, respectively. The suggested functions for these miRs could be important for the number of oligodendrocytes and astrocytes that is reportedly reduced in BA24 of familial BD and MDD patients and a potential target of anti-BD medications including lithium and antidepressants. To verify these putative candidates and to discover novel, we will under Specific Aim 1 employ Next Generation Sequencing (NGS, RNA Seq) to examine currently collected CSF and plasma samples from patients diagnosed with BD, MDD, and healthy subjects. These samples are being collected also under international Consortium on Lithium Genetics, the largest consortium ever to study the genetic underpinnings of response to lithium treatment in BD. The top novel BD exosomal miR biomarker candidate will be submitted to the same human tissue verification we performed for miR-29c and miR-149. Our preliminary data also suggest down-regulation of miR-29c and miR-149 in whole brain exosomes in a well-validated animal model of depression that features dysfunctional hippocampal astrocytes, flinders sensitive line (FSL) rat strain. We will also test our top NGS-emerged and tissue verified BD miR biomarker candidate in FSL brain exosomes. In Specific Aim 2 we will study the consequences of altered expression of miR-29c, miR-149 and of a verified NGS-emerged miR for the number and survival of glial cells and neurons in vivo and in vitro.

Together, the experiments under this proposal will not only test the putative BD biomarker candidates and yield new ones in the clinically accessible material, but also examine the link between BD neuropathology and its pathogenesis guiding future successful therapeutic interventions.