Do mood stabilizers interfere with epigeneti cs? Focus on the role of microRNAs (miRNAs) in the mechanism of acti on of lithium

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Mood stabilizers are widely used in the treatment and management of mood disorders. Among them, lithium represents the mainstay treatment to prevent mood episodes as well as suicidal behavior in bipolar disorder (BD) patients. The rate of response to mood stabilizers is significantly variable depending on the drug and in different studies, but there is robust agreement on that lithium is strongly effective in 30% of chronically treated patients with BD. The mechanism of action of mood stabilizers has been extensively investigated, especially for lithium. However, there is still uncertainty on what biological targets are key to the clinical efficacy of mood stabilizing drugs. Lithium response has been shown to be heritable, and it is known that genetics play an important role, but the complexity of the phenotype and the yet to be elucidated mechanism of action has hampered our understanding of the molecular modulators of lithium efficacy. Most of pharmacogenetics studies on mood stabilizers has explored the role of single nucleotide polymorphisms (SNP) or difference in gene expression levels in patients with different clinical response to treatments. Findings from these studies have pointed to intriguing and plausible players, but they also showed that the complexity of the mechanisms involved goes beyond sequence variants. A growing number of studies has explored the effect of mood stabilizers on epigenetic targets. Epigenetics involves potentially reversible modifications in chromatin structure and regulation that ultimately regulate gene expression. Among mood stabilizers, valproate is a well-known inhibitor of histone deacetylase (HDAC), but several studies now support a role of other mood stabilizers in modulating epigenetic targets. Lithium has been shown to interfere with the expression of several microRNAs (miRNA), small molecules of non-coding RNAs involved in regulating gene expression. In this symposium, data on the effect of mood stabilizers on epigenetic targets will be presented, particularly focusing on lithium. In a recent genome wide study, we showed that lithium influences the expression of two miRNAs in lymphoblasts derived from BD patients who committed suicide, and that the expression of these miRNAs is influenced by in vitro lithium treatment in neural precursors derived from induced pluripotent stem cells. Moreover, one of the two miRNAs (miR-4286) showed altered expression in postmortem brains

from BD subjects compared to healthy controls. In silico analyses showed that the two miRNAs regulate genes and proteins part of key processes in cellular functioning, as supported by gene ontology and pathways analyses performed on the predicted targets of these miRNAs. Overall, findings suggest that epigenetic modifications may play a key role in modulating the effect of mood stabilizers, adding an important piece to the puzzle of their molecular targets, and providing valuable insights that could help us dissecting the high heterogeneity in response to mood stabilizing treatments.