Examining the role of epigenetic modifications in the Autism Spectrum Disorders (ASD)

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Autism Spectrum Disorders (ASD) are heterogeneous neurodevelopmental disorders characterized by impaired communication and social interactions, as well as by obsessive and repetitive behaviors[1]. While a large percentage of autism cases are of unknown origin, various studies have identified several mutations in genes involved in histone modification as well as DNA methylation, pinpointing epigenetic mechanisms as key players in the development of ASD[2,3,4]. The importance of epigenetic modifications in ASD etiology were further underscored by studies into reported cases of ASD in patients arising from maternal administration of valproic acid (VPA), a chemical inhibitor of histone deacetylase activity, during pregnancy[5]. Using VPA as a model of epigenetic modifications in autism, we examined the effect of VPA treatment on long-term synaptic activity in male and female stem cell derived cortical neurons by multi-electrode array (MEA) analyses and immunocytochemical staining. We also assessed VPA-induced transcriptome wide changes in these neurons by RNA-seq and found significant upregulation in genes associated with epigenetic regulation and autism, one of which encodes ASH1L, a histone methyltransferase that we also show is involved in neurite outgrowth through BDNF/TrKB signaling. Our results demonstrate the close relationship between alterations in epigenetic modification and disruptions in synaptic connectivity and cell signaling that have come to be associated with ASD.

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