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Modeling Epigenetic Variation linked to Opioid Use Disorder in iPSC-derived Medium Spiny Neurons

Opioid addiction remains a major public health crisis in the United States. Genome-wide association studies (GWAS) of Opioid Use Disorder (OUD) have identified risk primarily within the noncoding genome, suggesting an important role for regulatory mechanisms. The genetic and environmental basis of OUD highlights that epigenetic regulation plays a central role in disease risk. In our laboratory, we investigate how OUD alters the brain's epigenetic landscape.

We previously analyzed postmortem nucleus accumbens (NAc) tissue from over 100 opioid overdose cases and accidental death controls using H3K27ac ChIP-seq. These studies revealed individual-specific epigenetic variation in opioid overdose cases, which we term Variant Enhancer Loci (VELs). By integrating Hi-C chromatin interaction data, we linked putative enhancer regions to their target genes and identified novel candidate genes implicated in OUD. Gene ontology and enrichment analyses of these genes revealed a significant overrepresentation of splicing-related pathways, highlighting RNA regulation as a potential mechanism. One candidate gene emerging from this analysis is CELF5, an RNA-binding protein involved in alternative splicing.

To investigate the functional role of CELF5, we use a stem cell-derived model of medium spiny neurons (iMSNs), the predominant neuronal cell type in the NAc. Knockdown of CELF5 in iMSNs resulted in downregulation of extracellular matrix (ECM)-related transcripts, implicating CELF5 in pathways related to neuronal structure and signaling.

We are also examining how opioid exposure contributes to epigenetic changes associated with OUD. By treating iMSNs with opioids, we aim to determine whether enhancer alterations arise from drug exposure or reflect underlying genetic vulnerability. Given the frequent contribution of fentanyl to overdose deaths, this model provides a powerful system to study molecular changes influencing brain reward circuitry and drug response. Together, this work seeks to elucidate the molecular mechanisms linking epigenetic regulation and neuronal function in OUD.

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