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**Angiogenic Gene Networks are Dysregulated in Postmortem Brain of Opioid Use Disorder Subjects: Evidence from Multi-Omics and Imaging Approaches**

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Opioid use disorder (OUD) is a public health crisis in the U.S. that causes over 50 thousand deaths annually due to overdose. Therefore, understanding the molecular effects of OUD is critical in this time of widespread opioid use. We used next-generation RNA sequencing and proteomics techniques to test the hypothesis that OUD causes differential regulation of gene networks in dorsolateral prefrontal cortex (Brodmann Area 9, or BA9) of human brain. We identified 394 differentially expressed (DE) coding and long noncoding (lnc) RNAs as well as 213 DE proteins in BA 9 of OUD subjects. The RNA and protein changes converged on pro-angiogenic gene networks and cytokine signaling pathways. Four genes (LGALS3, SLC2A1, PCLD1, VAMP1) were dysregulated in both RNA and protein. Dissecting these DE genes and networks, we found cell type specific effects with enrichment in astrocyte and endothelial correlated genes. Weighted-genome correlation network analysis (WGCNA) revealed cell type correlated networks including an astrocytic/endothelial network involved in angiogenic cytokine signaling as well as a neuronal network involved in synaptic vesicle formation. In addition, using an innovative *ex vivo* imaging approach, we identified increased vascularization in postmortem brains from subjects with OUD. This is the first study of its kind relating dysregulation of astrocytic and endothelial angiogenic gene networks in OUD with imaging evidence of hypervascularization in postmortem brain.