Name: Ryan Logan Email: ryan.logan@umassmed.edu

Elevated DNA damage and inflammatory markers in specific striatal cell types associated with opioid use disorder using single nuclei RNAseq in human postmortem brain

BaDoi Phan[1], Madelyn Ray[2], Marianne Seney[3], Jill Glausier[3], David Lewis[3], Andreas Pfenning[1], and Ryan Logan[2,4,5]

[1]Department of Computational Biology, Carnegie Mellon University, Pittsburgh, PA; [2]Department of Pharmacology and Experimental Therapeutics, Boston, MA; [3]Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA; [4]Department of Psychiatry and [5] Department of Neurobiology, University of Massachusetts Chan Medical School, Worcester, MA

To date, we have a limited understanding of the cellular and molecular changes in brains of people with opioid use disorder (OUD). The dorsal striatum is implicated in opioid craving and relapse in OUD. To address this limitation, the current study used single nuclei RNA-sequencing of dorsal striatum from postmortem brains of subjects with OUD. Nuclei extracted from postmortem dorsal striatum (n=12 subjects, 3 per sex per unaffected vs. OUD) were processed for RNA-sequencing using 10X Genomics platforms. Sequencing data was aligned (STARsolo) and processed for QC (ambient mRNA detection and correction; empy droplet and doublet filtering). Dorsal striatum of non-human primate single cell datasests were used for cell annotation transfers to cluster cell types. Modified limma models were used to identify differentially expressed genes (DEGs; FDR<0.05) and other analysis included area-under-curve marker enrichments to characterize DNA damage signatures by cell type. Significant DEGs were identified for each of the major cell types, including astrocytes, microglia, endothelial cells, oligodendrocytes, and specific neuronal subtypes, such as DRD1, DRD2, and interneuron subclasses. Sex-specific DEGs identified key genes related to OUD. Enrichment analyses highlighted pathways related to neuroinflammation, aging, and cellular stress. Higher proportions of DNA damage markers were found in OUD subjects compared to unaffected. DNA damage scores were primarily elevated in glial subtypes and interneurons. Overall, our results identify significantly alterations in pathways related to inflammation and DNA damage in specific cell types associated with OUD.