Linking brain cell types with predisposition to alcohol consumption in rats

Laura Saba[1], Chongyuan Luo[2], Cuining Liu[2], Melinda Dwinell[3], Spencer Mahaffey[1], Paula Hoffman[4], Boris Tabakoff[5]

[1]Department of Pharmaceutical Sciences, University of Colorado Anschutz Medical Campus, Aurora, CO, USA. [2]Department of Human Genetics, University of California Los Angeles, Los Angeles, CA, USA. [3]Department of Physiology, Medical College of Wisconsin, Milwaukee, WI, USA. [4]Department of Pharmacology, University of Colorado Anschutz Medical Campus, Aurora, CO, USA. [5]Institute for Behavioral Genetics, University of Colorado Boulder, Boulder, CO, USA.

Alcohol Use Disorder (AUD) cannot occur without the consumption of alcohol, and both its prevention and treatment depend on knowledge of the biological (e.g., genetic) and environmental factors that promote “heavy drinking”. Here we focus on the genetic components that predispose the phenotype of voluntary alcohol consumption and the role of different cell types from the rat prefrontal cortex (PFC), a brain region linked to self-regulation of drug taking behaviors. We applied single-nucleus methylcytosine and transcriptome sequencing (snmCT-Seq) to rat PFC samples from the two inbred strains that are progenitors of the HXB/BXH RI panel and represent significant genetic divergence. Cells were clustered using both modalities simultaneously (“joint clustering”) and clusters were assigned cell-type labels based on previously published marker genes. A total of 2,282 nuclei passed quality control for both modalities. Significant between-strain differential RNA expression was observed in 8 clusters across 177 unique genes and differential CpG-methylation at the cytosine level was detected in every cluster. In addition, the Scissor algorithm was used to link alcohol consumption from >20 HXB/BXH recombinant inbred strains with individual cells/nuclei in the single cell/nuclei RNA-Seq dataset from the 2 progenitor strains through bulk whole brain RNA-Seq data in the HXB/BXH strains from the PhenoGen website (https://phenogen.org/). This algorithm identified 222 Scissor+ cells, i.e., cells relevant to alcohol consumption. Oligodendrocytes were the most enriched cell type with almost 80% of oligodendrocyte cells identified as Scissor+. Likewise, oligodendrocytes have been identified as cells of interest in previous published work with human post mortem tissue from alcohol dependent and control individuals. Understanding the biological mechanisms that link genetic factors to excessive consumption of ethanol allows for development of molecular/pharmacological strategies for both prevention and treatment. Supported by NIH (R24AA013162 [LS, BT, PH]; R24OD024617 [MD]; U01DA051937 [LS]; P30DA044223 [LS]).