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Role of GSCAN Identified Genes in the Astrocytic Response to Nicotine

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Recent work has implicated a role for astrocyte function in nicotine neurobiology. To identify astrocyte-expressed genes that may be relevant to nicotine use in humans, we used TWAS results from the GWAS & Sequencing Consortium of Alcohol and Nicotine use (GSCAN) along with astrocyte expression data to identify genes of interest (GOI) to assess potential astrocyte involvement in nicotine responses. Using a CRISPR knockout approach to knock down GOI expression, we are screening 25-50 GSCAN-identified genes that show expression in human and mouse astrocytes. Using area analysis, we are assessing the role of the GOI on astrocyte size and morphology in primary mouse astrocytes following nicotine treatment. Previously, we found that Akt2 expression is restricted to astrocytes in mice and humans and may play a role in the nicotinic responses of astrocytes. Behavioral assessments of astrocyte specific Akt2 deficient mice were conducted, revealing impacts of AKT2 loss on behaviors relevant to nicotine use providing proof of principle results for our ongoing GOI studies. We have also found Clusterin to be a promising target and generated a Clusterin KO mice colony. Initial acute nicotine data suggests a role for Clusterin in the astrocytic nicotine response. In vivo chronic, acute nicotine, and behavioral studies are planned to confirm Clusterin KO affects astrocytic response, and behavioral studies have been completed. These results will allow for the identification of potential novel drug targets and will improve the current understanding of the astrocytic response to nicotine.