The Neuropathology of Alcohol Use Disorder

Authors:
Greg T. Sutherland[1], H-T Nguyen-Hao[1], Caine C. Smith[1], Wei Xin Ong[1]

[1]Sydney Brainomics, School of Medical Sciences, Faculty of Medicine and Health, The University of Sydney, Sydney, Australia.

Presenter's email: g.sutherland@sydney.edu.au

Introduction: The chronic heavy or binge alcohol consumption seen with alcohol use disorder (AUD) damages the structural and functional integrity of the brain, leading to alcohol-related brain damage (ARBD). This damage underpins both addiction and neurodegeneration associated with in AUD. Our studies with human postmortem tissue have shown that ARBD is characterised by widespread white matter loss and lipidomic abnormalities. We have demonstrated gliosis in cortical white matter but no changes in glial cell density. Single cell data has confirmed an aberrant immune response in AUD, where activated microglia likely induce reactive astrocytes.

Methods: In the current work we have extended these studies in postmortem brain tissue to include lipidomics and a new molecular technology called spatial transcriptomics to better characterise gliosis in AUD.

Results: A microglial subtype promotes astrocytic ILβ and TGF-β1 signalling that induces downstream lipid anomalies in myelin and eventual senescence of oligodendrocytes in brain regions most susceptible to ARBD. We further demonstrate associations between ARBD, lifetime alcohol consumption and the extent of liver damage.

Discussion and conclusions: Our work reveals markers that can be used to judge the severity of ARBD in human brain tissue. The central role of gliosis in ARBD suggests that immunomodulatory therapies that interrupt pro-inflammatory glial-glial signalling can halt the loss of myelin, allowing repair of white matter changes and the reversal of AUD.

Disclosure of Interest Statement: This work was supported by the National Institute on Alcohol Abuse and Alcoholism (R28AA012275 and R01AA028408).