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Therapeutic Inhibition of Molecular Drivers of Microglial Reactivity in Neurodegenerative Disease

It is estimated that over 55 million people have Alzheimer's disease (AD) or other dementias, and despite their rapidly increasing burden, thus far there are no disease modifying therapeutics available. Novel therapeutic strategies are urgently needed to address the prevention and treatment of AD. Mounting evidence from large scale genetic studies of risk have suggested that microglial activation and subsequent neuroinflammation is a critical causal component of AD onset and progression. Recent technological advances can now enable transcriptomic profiling at the resolution of individual cells, offering a sophisticated view of brain cell types, including microglia.

Researchers at Arizona State University in collaboration with Dr. Reiman at Banner Health studied postmortem cortical tissue samples from 101 subjects from the Arizona Study of Aging and Neurodegenerative Disorders/Brain and Body Donation Program (BBDP) to better understand the gene regulatory networks that are drivers in neurodegenerative disease-associated microglial changes. They identified an antisense transcript, which appears to be responsible for the dynamic rewiring of the microglial gene regulatory network observed in AD. This antisense transcript has not previously been described in the context of microglial biology or AD. Suppression of this antisense transcript could dampen the reactivity of microglia undergoing exogenous perturbation and temper the deleterious effects of microglial activation on neighboring cells.

This antisense transcript appears to be a key molecular driver in AD associated microglia and therapeutic inhibition of it could modulate microglial reactivity in neurodegenerative disease.

Potential Applications

- Therapeutic inhibition of molecular drivers of microglial reactivity in neurodegenerative disease
  - Alzheimer's disease
  - Other neurodegenerative diseases with microglial reactivity

Benefits and Advantages

- Could inform the design of AD or neurodegenerative disease relevant therapeutics
- Could attenuate microglial activation to reduce neuroinflammation
- Strong computational evidence supporting the therapeutic interest of this transcript
- Illuminates novel disease biology in AD and potentially other neurodegenerative diseases
- The brain tissue was exceptionally high quality with well characterized donors with and without clinical and neuropathological features of AD
- The data was analyzed in a supervised, targeted approach, applying DAseq for rich complex analyses in a manner not biased by inter-individual differences in cell type fractions

For more information about this opportunity, please see

Wang et al - bioRxiv - 2023