Modulating Neuron and Oligodendrocyte Survival by Targeting Astrocyte-Secreted Neurotoxic Lipids and Lipoproteins

Technology

The Liddelow Lab has demonstrated a connection between neurotoxic astrocytes (a type of glial cell that is important for neuronal survival, synapse formation, and control of neurotransmitter release) and neuronal cell death that is modulated by long-chain lipids, The connection suggests a new approach to treating multiple neurodegenerative diseases and CNS injury. The researchers sought to understand astrocyte-mediated toxicity by purifying proteins that mediate the process. Surprisingly, toxicity was shown to be carried out by lipids and lipoproteins. Moreover, lipoparticles that contain the ApoE/ApoJ apolipoproteins were necessary for astrocyte-mediated toxicity. Lipidomics and metabolomics further showed that toxic astrocytes have an upregulation of long-chain, saturated free fatty acids and very-long chain phosphatidylcholines (PCs). Moreover, the enzyme that catalyzes the elongation of free fatty acid (FFA) chains in the brain, ELOVL1, was found to be the upstream regulator of the neurotoxic astrocyte phenomenon.

Background

Neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease, and amyotrophic lateral sclerosis (ALS), are extremely common in the elderly population (especially AD at about 30% prevalence over the age of 85). The economic burden in the US is around $200 billion in healthcare costs and lost productivity. Despite extensive research efforts, the exact mechanisms of neurodegenerative diseases is still debated and no curative treatments are available.

Applications

- ApoE/ApoJ and ELOVL1 are targets for drug screening efforts, either biologics or small molecules. ApoE/ApoJ were previously shown to be upregulated in a number of brain injuries and ailments and this study helps explain that connection.
- Enzymatic levels of ELOVL1 in the brain could be used to diagnose the severity of CNS diseases and injuries.

Advantages

Category

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Life Sciences/Therapeutics/Neurodeg

Diseases

Authors

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- **Not disease-specific:** The novel pathway involved in the activation neurotoxic astrocytes that kill neurons and oligodendrocytes presents an exciting new target for treating multiple diseases that have no effective cure.
- **Tissue-specific target:** The ELOVL1 elongase is the only elongase found in astrocytes and the main one in the brain.
- **Expands potential therapeutic targets:** A shift in focus from secreted proteins to lipid metabolism in astrocytes is likely to result in more therapeutic targets and components that take part in the neurotoxicity.

Intellectual Property

U.S. non-provisional and European applications pending

References

1. Guttenplan, K.A., Weigel, M.K., Prakash, P. et al. , https://www.nature.com/articles/s41586-021-03960-y