SorCS2 deficiency sensitizes astrocytes to amyloid-beta and accelerates Alzheimer's pathology

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder leading to memory loss, cognitive impairment, and structural changes in the brain. One of the main drivers of neuronal dysfunction and death in AD is the accumulation of toxic amyloid-β deposits in the brain. While the role of astrocytes in AD pathology is increasingly recognized, the exact mechanisms by which these cells influence neurodegeneration have remained unclear.

Here, we demonstrate that an impaired astrocytic response to amyloid-β-induced stress plays a critical role in the development of pathological changes in a mouse model of AD. We found that in mice lacking SorCS2 - a protective protein produced by astrocytes -even low levels of amyloid-β triggered astrocyte reactivity. This led to neuroinflammation as well as heightened deposition of both amyloid-β and tau protein, which are hallmarks of AD progression.

Furthermore, we showed that this abnormal astrocytic response to amyloid-β activates δ-secretase, a stress-induced protease involved in generating pathogenic forms of both amyloid-β and tau. Overall, our findings indicate that an aberrant response by astrocytes to amyloid-β drives the accumulation of pathogenic protein aggregates in the brain, marking a pivotal process in the progression of Alzheimer's disease.