News Release

Title

Deficiency of a sulfotransferase for sialic acid–modified glycans mitigates Alzheimer's pathology

Key Points

- Microglial expression of sialic acid-modified keratan sulfate, an extracellular glycan molecule, correlates with Aβ pathogenesis in AD mouse models and patients with AD.
- GlcNAc6ST1 is the sialic acid-modified keratan sulfate sulfotransferase and regulates microglial Aβ phagocytosis and cytokine responses.
- GlcNAc6ST1 deficiency attenuates AD brain pathology.
- Inhibition of the keratan sulfate synthesis in microglia by targeting GlcNAc6ST1 may be a beneficial approach to ameliorate AD pathogenesis.

Summary

Alzheimer's disease (AD) is characterized by deposition of extracellular amyloid-β (Aβ) plaques and memory dysfunction. The authors demonstrated that sialic acid-modified keratan sulfate (KS) is upregulated in microglia of the brains of transgenic mice and in postmortem brain samples from AD patients. Subsequently, the authors identified GlcNAc6ST1 as a sulfotransferase essential for the microglial sialic acid-modified KS in AD. The authors crossbred GlcNAc6ST1-deficient (GlcNAc6ST1$^{-/-}$) mice with J20 transgenic mice, a model of AD. In primary microglia cells from the resulting J20/GlcNAc6ST1$^{-/-}$ mice, the authors found increased levels of Aβ phagocytosis and a hyper-active response to interleukin-4, an anti-inflammatory cytokine. Moreover, the mice exhibited reduced levels of cerebral Aβ plaques. The findings suggest that GlcNAc6ST1 might regulate microglial function by synthesizing sialic acid-modified KS. According to the authors, inhibition of the KS synthesis by targeting GlcNAc6ST1 might provide a therapeutic approach for mitigating AD pathogenesis.

Research Background

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that is characterized by deposition of extracellular amyloid-β (Aβ) plaques and memory dysfunctions. Microglia, a type of myeloid cell population and are brain-resident immune cells, directly phagocytose Aβ plaques and are indirectly involved in clearance of plaques as they release various cytokines. Keratan sulfate (KS) is an extracellular glycan present in neural tissues including the brain. The cell-surface KS has been suggested to play a role in microglial functions by binding via interactions with carbohydrate-binding receptors and molecules such as sialic acid-binding immunoglobulin-like lectins (siglecs) and galectins. Regulatory roles of microglial KS in neurodegenerative diseases such as AD have long been unclear, however. Here, we found that the sialic acid-modified KS is induced in microglia in mouse models and in patients with AD. Moreover, the KS glycan and its synthetic enzyme, GlcNAc6ST1, are shown to regulate the pathogenesis of AD via microglial cellular functions.

Research Results

The authors show that a type of KS with a certain molecular mass and sialic acid modification in microglia and its synthetic enzyme GlcNAc6ST1, previously known as a sulfotransferase for ligands of L-selectin, are

upregulated in model mice and patients with Alzheimer's disease. GlcNAc6ST1 deficiency resulted in increased amyloid-β phagocytosis and hyperresponsiveness to an anti-inflammatory cytokine in primary microglia. Moreover, amyloid-β pathology was mitigated in GlcNAc6ST1-deficient Alzheimer's model mice.

Research Summary and Future Perspective

These data support a model in which GlcNAc6ST1 regulates microglial functions via synthesizing sialic acid–modified KS, a potential ligand for microglial carbohydrate-recognizing receptors such as CD33-related siglecs, in Alzheimer's pathology. Inhibition of KS synthesis in microglia by targeting GlcNAc6ST1 might provide a therapeutic approach for mitigating AD pathogenesis.

Publication

Zhang Z, Takeda-Uchimura Y, Foyez T, Ohtake-Niimi S, Narentuya, Akatsu H, Nishitsuji K, Michikawa M, Wyss-Coray T, Kadomatsu K, Uchimura K. Deficiency of a sulfotransferase for sialic acid–modified glycans mitigates Alzheimer's pathology. *Proceedings of the National Academy of Sciences of the United States of America,* published online on Mar.21, 2017.

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