Potential treatment of Alzheimer's disease astrocyte pathology based on nuclear lipid regulation

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The purpose of this perspective is to discuss the future development of a potential treatment of glial pathology in Alzheimer's disease (AD) and a new regulatory mechanism, nuclear lipids, which may be involved in the pathogenesis of the disease, based on the work of the authors (Takasugi et al., 2011; Komai et al., 2024).

Amyloid hypothesis: AD is a neurodegenerative disorder with progressive cognitive decline as its main complaint, and there has been a serious increase in the number of patients worldwide, posing a societal challenge. One of the major pathological features of AD is senile plaques, and their major component, small peptide amyloid-β peptide (Aβ), accumulates in the early stages of the disease and exerts aggregation toxicity. Therefore, the amyloid hypothesis, which considers Aβ to be the starting point of pathogenesis, is strongly supported. In fact, the U.S. Food and Drug Administration has approved aducanumab, lecanemab, and donanemab, which are antibodies against toxic extracellular Aβ, and light is beginning to shine on curative treatment of AD based on the amyloid hypothesis (Selkoe, 2024).

Glial pathology as a therapeutic target for AD and current limitations: However, these immunotherapies have side effects, including amyloid-related imaging abnormalities, and their therapeutic effects are limited to delaying the decline in cognitive function, so a definitive cure is still a long way off. One reason for this is that the onset of AD is related to changes in brain metabolism, such as changes in the lipid environment, and there is a problem that this pathological condition is not being followed up from this perspective. Another reason for this is that AD is a complex disease with multiple pathological states other than Aβ at the time of diagnosis, including intra-neuronal pathology, tau pathology, and glial pathology controlling neuroinflammation (Stanca et al., 2023; Takasugi et al., 2023). In addition to Aβ aggregation toxicity, it will be necessary to focus on these toxicities in future drug discovery research. Glial pathology in AD has been the focus of much attention, and a notable publication in Science reported that Bexarotene used for cutaneous T cell lymphoma, an agonist of the ligand-activated nuclear receptors, retinoid X receptor (RXR) markedly improved Aβ pathology by activating glial cells and increasing apolipoprotein E (ApoE) expression (Cramer et al., 2012). It should be noted that several study groups, including those cited in reference, published negative data (Veeraraghavalu et al., 2013), but in a proof-of-concept study of bexarotene using a small number of patients with AD, a reduction in Aβ burden was observed in many brain regions when patients with ApoE4, a risk genotype for AD, were excluded (Cummings et al., 2016). Such deviations between research groups or experimental subjects may be due to changes in the nature of glial cells in the model or the pathological environment of the individual, leading to differences in drug sensitivity. However, the signaling mechanisms that alter the regulation of gene expression and cause changes in cellular functions remain unclear.

Relationship between sphingosine kinase 2/sphingosine-1-phosphate signaling and amyloid-β metabolism: In the brain, sphingosine-1-phosphate (S1P), a signaling lipid, is primarily produced by sphingosine kinase 2 (SphK2). We previously showed that SphK2/S1P signaling regulates the activity of β-site APP cleaving enzyme-1 (BACE1), the rate-limiting enzyme for Aβ production in neurons. Treatment with SphK2 inhibitors or overexpression of the S1P degrading enzyme reduced BACE1 activity and, consequently, Aβ production. We also showed that SphK2 enzyme activity was increased in the brains of patients with sporadic AD, suggesting the involvement of neuronal S1P in AD pathogenesis (Takasugi et al. 2011). The fact that Aβ aggregation was significantly reduced in AD model mice under SphK2 knockout conditions also supports the link between SphK2/S1P and Aβ metabolism (Lei et al., 2019).

The physiological effects of S1P are diverse, including the regulation of cell proliferation and differentiation, inflammation, immunity, and neurological functions. Since S1P acts as a ligand for GPCRs, research has focused on its functions. Recently, however, S1P has been shown to have transcriptional regulatory functions in the nucleus. SphK2 shuttles between the cytoplasm and nucleus in response to the cellular environment and S1P is involved in various physiological responses, such as inflammation. Since abnormalities in lipid content and metabolism are known to be involved in the early pathogenesis of AD, the relationship between astrocytes, regulatory cells, and SphK2/S1P signaling is noteworthy.

Regulation of apolipoprotein E expression and astrocyte function by sphingosine kinase 2/sphingosine-1-phosphate signaling: Astrocytes are responsible for lipid metabolism in the brain, and their abnormal activation induces neuroinflammation, which is involved in AD pathology. In particular, ApoE, a major mediator of lipid transport in the brain, is mainly produced in astrocytes and has anti-inflammatory and Aβ-metabolizing effects. Ligand-activated nuclear receptors, RXR, and liver X receptor, which regulate the induction of ApoE expression, are useful therapeutic targets. However, given that ApoE secretion from astrocytes has been reported to be suppressed in AD (Mathys et al., 2019), and the reason why RXR agonists have not shown stable therapeutic effects in various studies, the presence of an unknown factor regulating RXR signaling and ApoE expression is expected.

We found that SphK2/S1P signaling is a suppressor of ApoE expression in human astrocyte-derived U87 cells and that co-treatment with an SphK2 inhibitor and RXR agonist enhanced ApoE expression compared with RXR agonist treatment alone. Furthermore, ATP binding cassette transporter A1 (ABCA1) and apolipoprotein J (ApoJ/clusterin), which are regulated by RXR as well as ApoE, are not affected by SphK2/S1P signaling, indicating that SphK2/S1P signaling specifically regulates ApoE expression. The regulatory mechanism of ApoE expression by SphK2/S1P signaling has also been observed in human primary astrocytes and mouse-derived hippocampal slices, indicating that this mechanism can be reproduced in several astrocyte models and is conserved among species (Komai et al., 2024). Additionally, we found that SphK2/S1P signaling also promotes inflammatory responses by activating the nuclear factor-κB pathway and enhancing the expression of proinflammatory cytokines in astrocytes. Since SphK2/S1P signaling regulates ApoE expression at the transcriptional level, it was expected to function in the nucleus. Interestingly, it has been reported that the nuclear localization of SphK2 is increased in AD brains (Dominguez et al., 2018), suggesting a nuclear function of S1P in AD pathogenesis. We analyzed the subcellular localization of SphK2 in U87 cells and found that SphK2 is abundant in the nucleus. Then, chromatin immunoprecipitation analysis showed that SphK2/S1P signaling functions as a modulator that inhibits RXRα binding to the APOE promoter region. Although further analysis is needed, a more complex nuclear regulatory mechanism is expected, given that SphK2/S1P signaling affects ApoE expression, but not ABCA1 and ApoJ. Finally, we analyzed the effects of increased ApoE expression by SphK2 inhibition on Aβ metabolism and found that the increased ApoE upon co-treatment with the SphK2 inhibitor and RXR agonist promoted ApoE receptor-mediated Aβ metabolism compared with RXR agonist treatment alone. Consequently, our study suggests the new function of nuclear S1P in astrocytes and demonstrates that SphK2/S1P signaling is a novel therapeutic target that simultaneously regulates Aβ production in neurons, inflammation, and Aβ metabolism in astrocytes (**Figure 1**).

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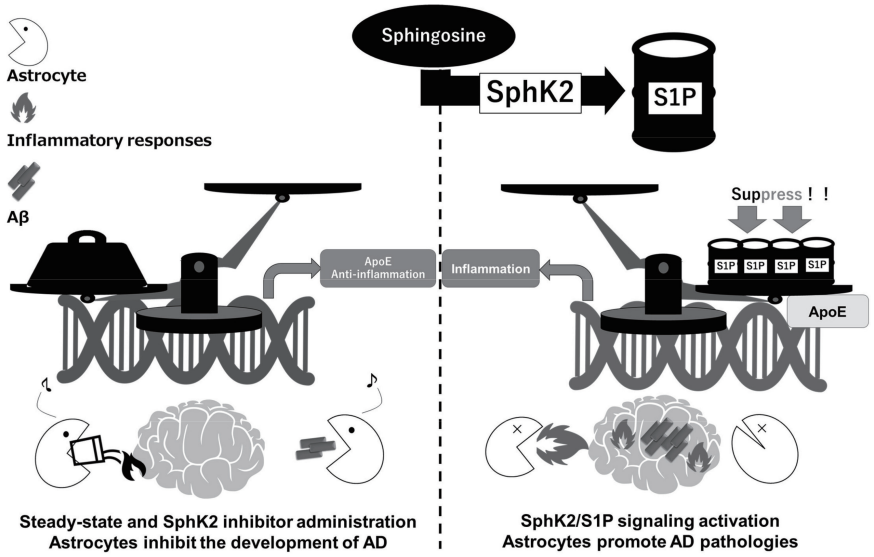

Figure 1 | **Schematic view of our work.**
SphK2 activation "switches" astrocyte function from disease-protective to progressive via nuclear S1P signaling. AD: Alzheimer's disease; ApoE: apolipoprotein E; Aβ: amyloid-β peptide; S1P: sphingosine-1-phosphate; SphK2: sphingosine kinase 2.

Conclusion and prospects: It must be pointed out that our study has some limitations. One is the concern about side effects, with atrophy and demyelination in the hippocampus reported in SphK2 knockout conditions (Lei et al., 2019), and with RXR agonists, there is concern about the risk of vascular damage from increased triglycerides in the blood (Cummings et al., 2016). We found that SphK2 inhibitors and RXR agonists may work in concert to increase ApoE expression and reduce the dose of each drug. Future *in vivo* models should be tested to determine whether these side effects can be overcome.

Second, ApoE has three isoforms, ApoE2, ApoE3, and ApoE4, and this study focuses on ApoE3. It should be considered that ApoE4, a known risk factor for AD, was not examined in this study, and additional validation from this perspective may be needed in the future to demonstrate whether this pathway is a therapeutic target.

Third, some part of the mechanism by which SphK2/S1P regulates ApoE remains to be elucidated. After the publication of our study, it was reported that SphK2 and S1P have been reported to interact with one of the nuclear receptors, aryl hydrocarbon receptor, and regulate its nuclear translocation (Yokoyama et al., 2024). Further verification is required to determine whether the reported mechanism correlates with ApoE expression; however, this paper reports that multiple LxLL motifs in SphK2 are interaction sites with aryl hydrocarbon receptor, and it is an interesting coincidence that RXRα and other proteins have also been reported to interact with LxLL motifs through a similar mechanism (Delerive et al. 2002). Since S1P is a short-lived signaling factor, and many of the factors that interact with SphK2 exhibit S1P-binding properties, we are currently searching for regulators of ApoE from the SphK2 interactome.

In general, there are many unknowns about the functions of lipids in the nucleus, and elucidation of the detailed molecular mechanisms may provide information on their relevance to pathological conditions and their effectiveness as therapeutic targets. Although this study focused on AD treatment, it may lead to more diverse pathological elucidation, considering that S1P functions in the differentiation and maintenance of various cells, such as neurons, blood vessels, and immune cells.

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COMMENTS TO AUTHORS

The information of the manuscript entitled "Potential Treatment of Alzheimer's disease astrocyte pathology based on nuclear lipid regulation" is interesting since it is an understudied field in dementia. Also the main aim in interesting: "The purpose of this Perspective is to discuss the future development of a potential treatment of glial pathology in Alzheimer's disease (AD) and a new regulatory mechanism, nuclear lipids, which may be involved in the pathogenesis of the disease, based on the work of the authors (Komai et al. 2024; Takasugi et al. 2011)."

1- However, the manuscript is initiated by describing the amyloid hypothesis of AD, when the described results and purpose is approaching a new perspective. Therefore, that the limitations of those anti amyloid treatments and problems and even deaths that have arised in some treated patients should be discussed, and how the amyloid hypothesis is hindering other hypothesis including the one indicated in the present work: the lipid dyshomeostasis in dementia.

2- The following sentence needs to be rephrased:

"However, given that ApoE secretion from astrocytes has been reported to be suppressed in AD (Mathys et al. 2019), and furthermore, the reason why RXR agonists have not shown stable therapeutic effects in various studies, the presence of an unknown factor regulating RXR and ApoE expression is expected."

3- References should be included for the following sentence:

"The regulatory mechanism of ApoE expression by SphK2/S1P signaling has also been observed in human primary astrocytes and mouse-derived hippocampal slices, indicating that this mechanism can be reproduced in several astrocyte models and is conserved among species".