HIGH SCHOOL EDITION
Journal of Student Research
Volume 12 Issue 1 (2023)

Neuroprotective and Detrimental Effects of Astrocytes On Amyloid Plaque Formation

Hao-Ran Gan[1], Jaime Grutzendler[#] and Edward Ziff[#]

[1]Hunter College High School, New York, NY, USA
[#]Advisor

ABSTRACT

In Alzheimer's disease (AD) brains, reactive astrocytes and microglia are frequently seen around amyloid plaques. The functions of microglia have been extensively studied, such as the neuroprotective barrier they form to prevent plaque growth and their release of inflammatory cytokines. However, the functions of astrocytes are less well known. Here I review the ongoing research on astrocytic functions around plaques. Recent studies suggest that astrocytes play an important role in downregulating Aβ production through the production of cholesterol and reducing plaque deposition through Aβ uptake and clearance. Astrocytes also interact with microglia through the clusterin and C3 pathways, possibly altering Aβ fibril formation and microglia phagocytosis. On the other hand, astrocytes contribute to elevated glutamate and GABA levels, potentially causing excitotoxicity and accelerating cognitive decline. Finally, I review two possible therapeutic treatments, ceftriaxone and selegiline, for alleviating AD pathology by targeting astrocyte functions. Given their crucial and complex roles in AD, a better understand of astrocyte functions would contribute to a greater understanding of AD progression and uncover new therapeutic targets.

Introduction

Alzheimer's disease (AD) is a neurodegenerative disease characterized by the accumulation of amyloid-β (Aβ) plaques and neurofibrillary tangles (NFT). The formation of Aβ plaques is caused by the cleavage of amyloid precursor protein (APP) and subsequent aggregation of Aβ oligomers. Aβ plaques are associated with dystrophic neurites such as atrophic dendrites and abnormal axonal varicosities, which likely contribute to neuronal circuit disruption (Gouras et al., 2014; Tsai et al., 2004; Yuan et al., 2022). Consistently, the extent of the cognitive impairment generally correlates with Aβ load and the number of plaques in the brain (Kok et al., 2022). Reducing Aβ load and amyloid plaques has been the major focus of research and therapeutic treatment in the past two decades (Karran et al., 2022; Vickers et al., 2016).

Reactive astrocytes and microglia are closely linked with plaques. Microglia are often found around plaques, where they form a neuroprotective barrier to limit plaque growth (Condello et al., 2015). Microglia also cause neuroinflammation and are associated with dystrophic neurites (Gomez-Isla and Frosch, 2022; Yang et al., 2021a). On the other hand, the role of astrocytes in plaque formation, growth, and neuronal damage is not as clear. They may interact with microglia and neurons around plaques to regulate plaque formation and neuronal damage (Kuchibhotla et al., 2009), but the detailed mechanisms underlying the astrocyte functions are generally unclear. In this paper, I review studies on the role of astrocytes in amyloid plaque deposition and how they are involved in neuroprotective functions, as well as neurotoxicity near amyloid plaques.

Function of Astrocytes in Regulating Aβ Production and Plaque Formation

Astrocytes are the most abundant cells in the brain and their processes occupy everywhere throughout the neuropil. Under many disease conditions, astrocytes are found to undergo substantial changes in protein expression and morphology. For example, astrocytes in amyotrophic lateral sclerosis (ALS) and stroke become hypertrophic and show high expression of glial fibrillary acidic protein (GFAP) (Harada et al., 2022; Kumar et al., 2021; Verkhratsky et al., 2019). Such reactive astrocytes are thought to be reprogrammed to increase neuroprotection of nervous tissue and restore homeostasis to the central nervous system (CNS) (Kumar et al., 2021; Verkhratsky et al., 2019). Around Aβ plaques, similar changes in astrocytes such as elevated GFAP levels have been observed (Pekny et al., 2016), indicating that astrocytes become reactive and may have an important role in regulating Aβ load and plaque growth in AD.

Astrocytes Regulate APP Processing and Aβ Levels.

One way astrocytes may alter plaque formation is by regulating APP processing and Aβ levels. APP is processed by three main secretases, α-secretase, β-secretase, and γ-secretase (Wang et al., 2021). α-secretase resides in disordered polyunsaturated lipids, while β-secretase and γ-secretase reside in lipid clusters on neurons (Wang et al., 2021). APP is usually cleaved by α-secretase to form a soluble APP fragment (sAPP-α), which controls neuronal excitability and does not contribute to plaque formation. However, occasional cleavage by the other two proteases results in toxic Aβ fragments that accumulate with disrupted lysosomal function (Lee et al., 2022; Raha et al., 2021).

APP processing is thought to involve the endocytosis of APP proteins into lipid clusters, where it is processed into Aβ peptides. Cholesterol regulates the formation of these lipid clusters, where β-secretase and γ-secretase reside (Wang et al., 2021). In the adult brain, most cholesterol is believed to be produced by astrocytes and transported by apolipoprotein E (apoE) to lipid clusters on neurons (Wang et al., 2021).

The effect of modulating cholesterol levels on APP processing has been investigated by depleting astrocytic cholesterol through the ablation of SREBP2 gene in a recent study by Wang et al (Wang et al., 2021). SREBP2 regulates cholesterol synthesis genes such as HMG-CoA reductase and HMG-CoA synthase (Madison, 2016). SREBP2 gene ablation significantly reduces the size of lipid clusters. Neither cholesterol depletion nor addition affects the trafficking of α-, β-, or γ-secretases in lipid clusters, suggesting that the enzymes remain static in the plasma membrane (Wang et al., 2021). Using ELISA to quantify Aβ40 and sAPP-α production under different levels of cholesterol revealed greater sAPP-α levels with low levels of cholesterol and greater levels of Aβ40 with higher levels of cholesterol. As the secretases remain unchanged in the plasma membrane, these findings suggest that APP moves to areas with α-secretase under low cholesterol conditions and neuronal lipid clusters with β-secretase and γ-secretase under high cholesterol conditions (Wang et al., 2021). Astrocytic cholesterol may therefore play a role in regulating Aβ production and plaque formation by controlling the ratio of sAPP-α to Aβ in the brain.

Astrocytes Are Involved in Aβ Uptake and Clearance

Another way astrocytes regulate plaque formation is through the uptake and clearance of Aβ40 and Aβ42. It has been shown that Nrf2 signaling, which is involved in protein homeostasis and detoxification, also regulates autophagy and plays a role in the astrocytic response to Aβ pathology (Jiwaji et al., 2022). In the mouse cortex and hippocampus, Nrf2 overexpression in astrocytes was found to reduce plaque density, number, and size (Jiwaji et al., 2022). Double-labeling of astrocytes and Aβ peptides revealed Aβ peptides in GFAP-positive astrocytes in APP/PS1xGFAP-Nrf2 mice, suggesting that Nrf2 may promote autophagy involved in Aβ clearance (Jiwaji et al., 2022). When the levels of Aβ40 and Aβ42 were compared between APP/PS1xGFAP-Nrf2 and APP/PS1 mice, a decrease in both oligomers was found in APP/PS1xGFAP-Nrf2 mice. No difference in expression of BACE1, a secretase enzyme responsible for the processing of APP, was found between APP/PS1

and APP/PS1xGFAP-Nrf2 mice, suggesting that lower levels of Aβ was not due to altered APP processing. In addition, p62 is a cargo protein often used as an index to measure astrocyte autophagy as it degrades after successful autophagic clearance (Jiwaji et al., 2022). Greater autophagy results in less p62 expression and vice versa. In APP/PS1xGFAP-Nrf mice with increased Nrf2 expression, lower levels of p62 accumulation were found (Jiwaji et al., 2022), suggesting that there was more p62 degradation and therefore more successful autophagic clearance. Together, these findings suggest that astrocytes may promote the uptake and clearance of Aβ through Nrf2-mediated autophagy.

Astrocytic regulation of plaque formation through the clearance of Aβ40 and Aβ42 could also be mediated by its secretion of the extracellular chaperone, clusterin (Clu). Clu binds to Aβ and is involved in Aβ deposition and clearance (Chen et al., 2021). In a study by Wojtas et al., a 50% reduction of Clu in Clu+/- heterozygous mice crossed with APP/PS1 mice was found to augment Aβ accumulation in brain parenchyma (Wojtas et al., 2020). On the other hand, viral-induced Clu overexpression in astrocytes by around 30% was found to substantially reduce insoluble Aβ40 and Aβ42 levels compared to APP/PS1 controls (Wojtas et al., 2020). Similarly, in a study by Chen et al., viral-induced Clu overexpression in astrocytes in 5xFAD mice also reduced the total number of amyloid deposits in the cortex and hippocampus (Chen et al., 2021). This reduced Aβ load could be explained by decreased Aβ fibril formation, as previous studies have shown that Clu forms complexes with Aβ and influences its solubility (Wojtas et al., 2020). Another possibility is increased microglial uptake of Aβ peptides, as lipidated Clu binds to TREM2, a gene that regulates neuroprotective functions such as phagocytosis by microglia (Chen et al., 2021; Condello et al., 2018). It is important to note, however, that global knockout of Clu in mice resulted in a decrease in total fibrillar plaques (Chen et al., 2021; Wojtas et al., 2020), contrary to how Clu reduction in astrocytes results in greater Aβ levels. This may be because the functions of Clu in the peripheral nervous system and/or other cell types such as microglia differ from those of astrocytic Clu.

Astrocytes Regulate Aβ Load By Interacting with Microglia.

Astrocytes are known to interact with microglia under many pathological conditions including AD (Yang et al., 2021b). As microglia are involved in neuroprotective processes around plaques, it is possible that astrocytes are involved in regulating plaque growth through interactions with microglia.

Microglia are dynamic immune cells in the CNS that respond rapidly to pathological lesions in the brain. Microglia have been found clustered around plaques (Condello et al., 2015; Yuan et al., 2016), where they anti-colocalize with hotspots of Aβ42 binding (Condello et al., 2015). When the CX3CR1 chemokine receptor was deleted in microglia, microglia proliferation around plaques increased and plaque size decreased (Liu et al., 2010). Conversely, a study by Zhao et al. demonstrated that microglia deletion resulted in an increase of plaque size (Zhao et al., 2017). Together, these findings suggest that microglia play an important role in limiting plaque size, potentially by forming a barrier to reduce Aβ binding and fibrillization. Consistent with this notion, in vivo imaging of fibrillar amyloid plaques revealed Aβ oligomers preferentially added to the side of plaques uncovered by microglia. It is worth noting that diffusion of Aβ oligomers into the plaque core occurs after injection, even with robust microglia coverage around the plaque (Condello et al., 2015). This suggests that the microglia barrier decreases affinity of soluble Aβ to the plaque but is not completely effective.

In addition to limiting growth, microglia coverage around plaques also results in compact rather than filamentous phenotype. Compact plaques are characterized by a distinct plaque core, surrounded by a halo of less compact amyloid. Filamentous forms are plaques that are less compact and typically have longer spike-like fibril branches (Yuan et al., 2016). Declines in microglia coverage caused by mutations of genes such as TREM2 result in a shift from compact to filamentous forms. This increases the average length of the diffuse fibrils and the surface to volume ratio of amyloid fibers by about 300% (Yuan et al., 2016). As a result, the

contact area between amyloid fibrils and neurites is increased, which may contribute to greater neurotoxicity and dystrophy (Yuan et al., 2016).

One major interaction between astrocytes and microglia involves C3, a protein in the complement system which mediates innate immunity (Lian et al., 2016). It is cleaved into the peptide C3a and the opsonin C3b (Lian et al., 2016). In a study by Lian et al., C3 RNA in situ hybridization and immunostaining with an anti-GFAP antibody revealed a strong colocalization between C3 mRNA and astrocyte GFAP in AD mouse models. C3a receptor (C3aR) RNA in situ hybridization and Iba-1 immunostaining further showed that microglia are the main source of C3aR (Lian et al., 2016).

As Aβ upregulates C3 protein expression, altered C3a levels in astrocytes on microglial functions via C3a-C3aR and plaque formation were tested in the APP/PS1 mouse model. C3a elevation resulted in significantly greater plaque deposition in the hippocampus and cortex of APP/PS1 mice (Lian et al., 2016). Quantifying Aβ40 and Aβ42 levels before plaque deposition as well as full-length APP showed no change (Lian et al., 2016), suggesting that there was no altered processing of APP, and that clearance was instead impaired. Furthermore, prolonged C3 treatment to microglia revealed an initial increase in phagocytosis, but a decrease after 24 hours. Consistently, reduced intracellular Aβ was found in microglial cultures after prolonged C3 treatment (Lian et al., 2016). Together, these results suggest that astrocyte exposure to Aβ leads to chronically elevated levels of C3a in astrocytes and impairs microglial phagocytosis, which results in increased Aβ accumulation and plaque formation.

Another interaction between astrocytes and microglia may involve the transmembrane protein PD-1 and its ligand PD-L1. PD-1, which is mostly expressed in microglia, regulates inhibitory function and T-cell activation in several autoimmune diseases, while PD-L1 is mainly expressed in astrocytes (Kummer et al., 2021). Kummer et al. observed that PD-1 deficiency in APP/PS1 mice increased soluble Aβ40 and Aβ42 levels as well as plaque number in the hippocampus and cortex, without significantly changing APP levels (Kummer et al., 2021). Measuring the uptake of fluorescently-labeled Aβ42 also revealed lower microglial uptake in PD-1-/- microglia, suggesting that the PD-1 is involved in Aβ clearance. PD-L1 deficiency in astrocytes was also tested by comparing microglia in an astrocyte-conditioned medium with WT versus PD-L1-/- astroglial cultures, similarly revealing decreased microglial uptake of Aβ. This could be explained by how PD-1 maintains CD36 expression, a gene involved in microglial uptake of Aβ (Kummer et al., 2021; Zinselmeyer et al., 2013). Together, these findings suggest that the PD-1/PD-L1 interaction between microglia and astrocytes is crucial in maintaining Aβ uptake. It is important to note, however, that PD-1 may only be expressed in microglia that are in close proximity to plaques, as the microglia that were closest to plaques showed the greatest expression of PD-1 (Kummer et al., 2021).

Astrocytes Contribute to Neurotoxicity Near Amyloid Plaques

Increased levels of both glutamate and GABA were observed around Aβ plaques, two of the main neurotransmitters that are associated with excitatory and inhibitory functions (Hefendehl et al., 2016; Mitew et al., 2013; Vickers et al., 2016). Dysregulation of these neurotransmitters may thus result in both hypoactive and hyperactive neurons, impairing synaptic transmission and thus cognitive ability.

Astrocytes Affect Glutamate Uptake Near Plaques

Astrocytes are essential in the uptake and release of glutamate via glutamate transporter-1 (GLT-1) and play a key role in removing excess glutamate from extracellular space into astrocytes (Hefendehl et al., 2016). In APP/PS1 mice, regions adjacent to plaque showed reduced GLT-1 expression (Hefendehl et al., 2016), suggesting potential impairment of glutamate clearance. Reduced glutamate uptake into astrocytes and subsequent

build-up of glutamate in extracellular space could lead to excessive activation of NMDA/AMPA receptors (Ovsepian et al., 2019; Verkhratsky et al., 2019) and consequently aberrant neuronal excitability. Furthermore, mice with heterozygous GLT-1 expression showed accelerated cognitive decline as well as an increase in the Aβ42/40 ratio with no significant change in total Aβ load (Mookherjee et al., 2011). These findings suggest that astrocytic uptake of glutamate is impaired around plaques, which may result in excitotoxicity and accelerate cognitive decline.

Astrocytes Release GABA Near Plaques

GABA is an inhibitory neurotransmitter that is mainly synthesized from glutamate through glutamic acid decarboxylase-67 (GAD67) and is released by astrocytes (Wu et al., 2014). In a study by Jo et al., GABA intensity in GFAP-positive astrocytes inversely correlated with the distance from the Aβ plaque. Between 20 and 80 μm, GABA intensity significantly increased. Beyond 80 μm, GABA intensity decreased to WT levels, suggesting that GABA levels are elevated in astrocytes near Aβ plaques (Jo et al., 2014). This is most likely a result of elevated production rather than reduced breakdown, as an investigation of the putrescine degradation pathway in GABA production revealed higher levels of Maob, the key enzyme involved in the production of GABA (Chun et al., 2020; Jo et al., 2014). This elevation may be a response to compensate for elevated levels of glutamate in the extracellular space. In the same study, excitatory postsynaptic currents (EPSCs) were measured to reveal that GABA inhibited synaptic transmission by decreasing the probability of neurotransmitter release. Antagonizing the GABA receptor improved both LTP and memory in AD mice (Jo et al., 2014). Together, these results suggest that elevated GABA production in astrocytes near Aβ plaques may result in excessive neuronal inhibition and consequently cause deficits in synaptic transmission. In addition to Aβ plaques directly causing neuronal dystrophy, both elevated GABA and glutamate levels as a result of reactive astrocytes around plaques may result in altered neuronal activity and ultimately contribute to the formation of dystrophic neurites.

Possible Astrocyte and Microglia Manipulation to Control Toxicity and Reduce Aβ Accumulation

As demonstrated above, astrocytes and their interactions with microglia regulate plaque load, Aβ production, and neuronal excitability through several factors, including cholesterol, clusterin, GABA, and glutamate. For example, GLT-1 downregulation around plaques causes increased glutamate levels and can result in excitotoxicity. Furthermore, GABA production in astrocytes is upregulated around plaques, which may cause excessive neural inhibition and accelerate AD pathology. Targeting these pathways may therefore serve as an approach in slowing the progression of AD.

The drug ceftriaxone has been reported to increase the expression of GLT-1 both in vitro and in vivo (Rothstein et al., 2005). Hefendehl et al. administered ceftriaxone to APP/PS1 mice. After treatment, GLT-1 expression within a 20μm radius of the plaque increased to the levels seen farther away (Hefendehl et al., 2016). This increased GLT-1 expression partially rescued glutamate clearance, leading to a significant reduction in the elevated glutamate levels normally seen around plaques. Ceftriaxone treatment also improved object recognition and performance in the Morris water maze (Hefendehl et al., 2016; Zumkehr et al., 2015). While the effect of ceftriaxone on Aβ plaque load was not measured, the rescue of glutamate dynamics may restore normal activity in hyperactive neurons and possibly alter Aβ deposition as well.

Another possible therapeutic treatment for AD is blocking GABA receptors or reducing GABA synthesis/release in astrocytes. As discussed above, reactive astrocytes around Aβ plaques excessively release GABA. This can cause increased tonic inhibition and impair neural transmission. In APP/PS1 mice, increased GABA was also found to impair memory compared to WT mice (Jo et al., 2014). Oral administration of the

drug selegiline to inhibit MAO-B, an enzyme involved in GABA synthesis, restored synaptic plasticity and memory (Jo et al., 2014). Reduction of GABA with selegiline could potentially alleviate AD pathology by normalizing the high level of GABA and restoring synaptic transmission associated with Aβ plaques.

Conclusion

In summary, recent studies have shown that astrocytes play both neuroprotective and detrimental roles in response to Aβ pathology. In particular, astrocytes regulate APP processing through cholesterol, mediate Nrf2 signaling to promote autophagy, and interact with microglia by releasing clusterin and C3a. However, reactive astrocytes have also been shown to contribute to elevated levels of both glutamate and GABA, which impairs synaptic transmission and induces excitotoxicity/excessive inhibition. Further studies on astrocyte functions are warranted in order to better understand their precise roles in AD pathogenesis. As astrocytes are involved in many Aβ-related processes, they present a promising target for therapeutic treatment of AD.

Acknowledgments

I thank Prof. Jaime Grutzendler at Yale University and Prof. Edward Ziff at New York University School of Medicine for their helpful advice and comments.

References

Chen, F., Swartzlander, D.B., Ghosh, A., Fryer, J.D., Wang, B., and Zheng, H. (2021). Clusterin secreted from astrocyte promotes excitatory synaptic transmission and ameliorates Alzheimer's disease neuropathology. Mol Neurodegener 16, 5. https://doi.org/10.1186/s13024-021-00426-7

Chun, H., Im, H., Kang, Y.J., Kim, Y., Shin, J.H., Won, W., Lim, J., Ju, Y., Park, Y.M., Kim, S., et al. (2020). Severe reactive astrocytes precipitate pathological hallmarks of Alzheimer's disease via H2O2(-) production. Nat Neurosci 23, 1555-1566. https://doi.org/10.1038/s41593-020-00735-y

Condello, C., Yuan, P., and Grutzendler, J. (2018). Microglia-Mediated Neuroprotection, TREM2, and Alzheimer's Disease: Evidence From Optical Imaging. Biol Psychiatry 83, 377-387. https://doi.org/10.1016/j.biopsych.2017.10.007

Condello, C., Yuan, P., Schain, A., and Grutzendler, J. (2015). "Microglia constitute a barrier that prevents neurotoxic protofibrillar Abeta42 hotspots around plaques." Nat Commun 6, 6176. https://doi.org/10.1093/brain/aww016

Gomez-Isla, T., and Frosch, M.P. (2022). "Lesions without symptoms: understanding resilience to Alzheimer disease neuropathological changes." Nat Rev Neurol 18, 323-332. https://doi.org/10.1186/s13073-023-01155-w

Gouras, G.K., Willen, K., and Faideau, M. (2014). The inside-out amyloid hypothesis and synapse pathology in Alzheimer's disease. Neurodegener Dis 13, 142-146. https://doi.org/10.1159/000354776

Harada, R., Furumoto, S., Kudo, Y., Yanai, K., Villemagne, V.L., and Okamura, N. (2022). Imaging of Reactive Astrogliosis by Positron Emission Tomography. Front Neurosci 16, 807435. https://doi.org/10.3389/fnins.2022.807435

Hefendehl, J.K., LeDue, J., Ko, R.W., Mahler, J., Murphy, T.H., and MacVicar, B.A. (2016). Mapping synaptic glutamate transporter dysfunction in vivo to regions surrounding Abeta plaques by iGluSnFR two-photon imaging. Nat Commun 7, 13441. https://doi.org/10.1038/ncomms13441

Jiwaji, Z., Tiwari, S.S., Aviles-Reyes, R.X., Hooley, M., Hampton, D., Torvell, M., Johnson, D.A., McQueen, J., Baxter, P., Sabari-Sankar, K., et al. (2022). Reactive astrocytes acquire neuroprotective as well as deleterious signatures in response to Tau and Ass pathology. Nat Commun 13, 135. https://doi.org/10.1038/s41467-021-27702-w

Jo, S., Yarishkin, O., Hwang, Y.J., Chun, Y.E., Park, M., Woo, D.H., Bae, J.Y., Kim, T., Lee, J., Chun, H., et al. (2014). GABA from reactive astrocytes impairs memory in mouse models of Alzheimer's disease. Nat Med 20, 886-896. https://doi.org/10.1038/nm.3639

Kok, F.K., van Leerdam, S.L., and de Lange, E.C.M. (2022). Potential Mechanisms Underlying Resistance to Dementia in Non-Demented Individuals with Alzheimer's Disease Neuropathology. J Alzheimers Dis 87, 51-81. https://doi.org/10.3233/JAD-210607

Kuchibhotla, K.V., Lattarulo, C.R., Hyman, B.T., and Bacskai, B.J. (2009). Synchronous hyperactivity and intercellular calcium waves in astrocytes in Alzheimer mice. Science 323, 1211-1215. https://doi.org/10.1126/science.1169096

Kumar, A., Fontana, I.C., and Nordberg, A. (2021). Reactive astrogliosis: A friend or foe in the pathogenesis of Alzheimer's disease. J Neurochem. https://doi.org/10.1111/jnc.15565

Kummer, M.P., Ising, C., Kummer, C., Sarlus, H., Griep, A., Vieira-Saecker, A., Schwartz, S., Halle, A., Bruckner, M., Handler, K., et al. (2021). Microglial PD-1 stimulation by astrocytic PD-L1 suppresses neuroinflammation and Alzheimer's disease pathology. EMBO J 40, e108662. https://doi.org/10.15252/embj.2021108662

Lee, J.H., Yang, D.S., Goulbourne, C.N., Im, E., Stavrides, P., Pensalfini, A., Chan, H., Bouchet-Marquis, C., Bleiwas, C., Berg, M.J., et al. (2022). Faulty autolysosome acidification in Alzheimer's disease mouse models induces autophagic build-up of Abeta in neurons, yielding senile plaques. Nat Neurosci 25, 688-701. https://doi.org/10.1038/s41593-022-01084-8

Lian, H., Litvinchuk, A., Chiang, A.C., Aithmitti, N., Jankowsky, J.L., and Zheng, H. (2016). Astrocyte-Microglia Cross Talk through Complement Activation Modulates Amyloid Pathology in Mouse Models of Alzheimer's Disease. J Neurosci 36, 577-589. https://doi.org/10.1523/JNEUROSCI.2117-15.2016

Liu, Z., Condello, C., Schain, A., Harb, R., and Grutzendler, J. (2010). CX3CR1 in microglia regulates brain amyloid deposition through selective protofibrillar amyloid-beta phagocytosis. J Neurosci 30, 17091-17101. https://doi.org/10.1523/JNEUROSCI.4403-10.2010

Madison, B.B. (2016). Srebp2: A master regulator of sterol and fatty acid synthesis. J Lipid Res 57, 333-335.

Mitew, S., Kirkcaldie, M.T., Dickson, T.C., and Vickers, J.C. (2013). Altered synapses and gliotransmission in Alzheimer's disease and AD model mice. Neurobiol Aging 34, 2341-2351. https://doi.org/10.1194/jlr.C066712

Mookherjee, P., Green, P.S., Watson, G.S., Marques, M.A., Tanaka, K., Meeker, K.D., Meabon, J.S., Li, N., Zhu, P., Olson, V.G., et al. (2011). GLT-1 loss accelerates cognitive deficit onset in an Alzheimer's disease animal model. J Alzheimers Dis 26, 447-455. https://doi.org/10.3233/JAD-2011-110503

Ovsepian, S.V., O'Leary, V.B., Zaborszky, L., Ntziachristos, V., and Dolly, J.O. (2019). Amyloid Plaques of Alzheimer's Disease as Hotspots of Glutamatergic Activity. Neuroscientist 25, 288-297. https://doi.org/10.1177/1073858418791128

Pekny, M., Pekna, M., Messing, A., Steinhauser, C., Lee, J.M., Parpura, V., Hol, E.M., Sofroniew, M.V., and Verkhratsky, A. (2016). Astrocytes: a central element in neurological diseases. Acta Neuropathol 131, 323-345. https://doi.org/10.1007/s00401-015-1513-1

Raha, S., Ghosh, A., Dutta, D., Patel, D.R., and Pahan, K. (2021). Activation of PPARalpha enhances astroglial uptake and degradation of beta-amyloid. Sci Signal 14, eabg4747. https://doi.org/10.1126/scisignal.abg4747

Rothstein, J.D., Patel, S., Regan, M.R., Haenggeli, C., Huang, Y.H., Bergles, D.E., Jin, L., Dykes Hoberg, M., Vidensky, S., Chung, D.S., et al. (2005). Beta-lactam antibiotics offer neuroprotection by increasing glutamate transporter expression. Nature 433, 73-77. https://doi.org/10.1038/nature03180

Tsai, J., Grutzendler, J., Duff, K., and Gan, W.B. (2004). Fibrillar amyloid deposition leads to local synaptic abnormalities and breakage of neuronal branches. Nat Neurosci 7, 1181-1183. https://doi.org/10.1038/nn1335

Verkhratsky, A., Rodrigues, J.J., Pivoriunas, A., Zorec, R., and Semyanov, A. (2019). Astroglial atrophy in Alzheimer's disease. Pflugers Arch 471, 1247-1261. https://doi.org/10.1007/s00424-019-02310-2

Vickers, J.C., Mitew, S., Woodhouse, A., Fernandez-Martos, C.M., Kirkcaldie, M.T., Canty, A.J., McCormack, G.H., and King, A.E. (2016). Defining the earliest pathological changes of Alzheimer's disease. Curr Alzheimer Res 13, 281-287. https://doi.org/10.2174/1567205013666151218150322

Wang, H., Kulas, J.A., Wang, C., Holtzman, D.M., Ferris, H.A., and Hansen, S.B. (2021). Regulation of beta-amyloid production in neurons by astrocyte-derived cholesterol. Proc Natl Acad Sci U S A 118. https://doi.org/10.1073/pnas.2102191118

Wojtas, A.M., Sens, J.P., Kang, S.S., Baker, K.E., Berry, T.J., Kurti, A., Daughrity, L., Jansen-West, K.R., Dickson, D.W., Petrucelli, L., et al. (2020). Astrocyte-derived clusterin suppresses amyloid formation in vivo. Mol Neurodegener 15, 71. https://doi.org/10.1186/s13024-020-00416-1

Wu, Z., Guo, Z., Gearing, M., and Chen, G. (2014). Tonic inhibition in dentate gyrus impairs long-term potentiation and memory in an Alzheimer's [corrected] disease model. Nat Commun 5, 4159. https://doi.org/10.1038/ncomms5159

Yang, A.J.T., Bagit, A., and MacPherson, R.E.K. (2021a). Resveratrol, Metabolic Dysregulation, and Alzheimer's Disease: Considerations for Neurogenerative Disease. Int J Mol Sci 22. https://doi.org/10.3390/ijms22094628

Yang, S., Magnutzki, A., Alami, N.O., Lattke, M., Hein, T.M., Scheller, J.S., Kroger, C., Oswald, F., Yilmazer-Hanke, D., Wirth, T., et al. (2021b). IKK2/NF-kappaB Activation in Astrocytes Reduces amyloid beta Deposition: A Process Associated with Specific Microglia Polarization. Cells 10. https://doi.org/10.3390/cells10102669

Yuan, P., Condello, C., Keene, C.D., Wang, Y., Bird, T.D., Paul, S.M., Luo, W., Colonna, M., Baddeley, D., and Grutzendler, J. (2016). TREM2 Haplodeficiency in Mice and Humans Impairs the Microglia Barrier Function Leading to Decreased Amyloid Compaction and Severe Axonal Dystrophy. Neuron 90, 724-739. https://doi.org/10.1016/j.neuron.2016.05.003

Yuan, P., Zhang, M., Tong, L., Morse, T.M., McDougal R.A., Ding, H., Chan, D., Cai, Y., Grutzendler, J. (2022). PLD3 affects axonal spheroids and network defects in Alzheimer's disease. Nature 612, 328–337. https://doi.org/10.1038/s41586-022-05491-6

Zhao, R., Hu, W., Tsai, J., Li, W., and Gan, W.B. (2017). Microglia limit the expansion of beta-amyloid plaques in a mouse model of Alzheimer's disease. Mol Neurodegener 12, 47. https://doi.org/10.1186/s13024-017-0188-6

Zinselmeyer, B.H., Heydari, S., Sacristan, C., Nayak, D., Cammer, M., Herz, J., Cheng, X., Davis, S.J., Dustin, M.L., and McGavern, D.B. (2013). PD-1 promotes immune exhaustion by inducing antiviral T cell motility paralysis. J Exp Med 210, 757-774. https://doi.org/10.1084/jem.20121416

Zumkehr, J., Rodriguez-Ortiz, C.J., Cheng, D., Kieu, Z., Wai, T., Hawkins, C., Kilian, J., Lim, S.L., Medeiros, R., and Kitazawa, M. (2015). Ceftriaxone ameliorates tau pathology and cognitive decline via restoration of glial glutamate transporter in a mouse model of Alzheimer's disease. Neurobiol Aging 36, 2260-2271. https://doi.org/10.1016/j.neurobiolaging.2015.04.005