The Role of Glial Cells and Synapse Loss in Mouse Models of Alzheimer’s Disease

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Synapse loss has detrimental effects on cellular communication, leading to network disruptions within the central nervous system (CNS) such as in Alzheimer’s disease (AD). AD is characterized by a progressive decline of memory function, cognition, neuronal and synapse loss. The two main neuropathological hallmarks are amyloid-β (Aβ) plaques and neurofibrillary tangles. In the brain of AD patients and in mouse models of AD several morphological and functional changes, such as microgliosis and astrogliosis around Aβ plaques, as well as dendritic and synaptic alterations, are associated with these lesions. In this review article, we will summarize the current literature on synapse loss in mouse models of AD and discuss current and prospective treatments for AD.

Keywords: Alzheimer’s disease, amyloid plaques, glial cells, synapse loss, microgliosis, astrocytes

SYNAPSE LOSS IN NEURODEGENERATION

Synapse loss has harmful effects on cellular communication, leading to network disruption in the central nervous system (CNS). The communication of billions of neurons within the mammalian brain generates and controls memory, thoughts and emotions. In a neuronal network with different cells, the transfer of information is coordinated at specialized compartments such as the synapse. Synapses are contact points between two neurons, where they communicate by passing ions or neurotransmitter across the synaptic cleft. Synapses can have excitatory or inhibitory effects on the target cells, depending on the released signals. The formed synapses are not rigid but rather dynamic and can either strengthen, shrink or even get lost. Considering the critical role of synapses under physiological conditions, it is not surprising that a severe loss of synaptic integrity can cause substantial disorders such as neurodegenerative diseases (Dudai and Morris, 2013).

Neurodegenerative diseases are disorders of the CNS or the peripheral nervous system characterized by the progressive structural and functional degeneration of neurons, leading to mental or movement problems. The most common form of neurodegenerative diseases is Alzheimer’s disease (AD) which currently affects 46 million people worldwide (Prince, 2015). Over a century ago Alois Alzheimer first described the defining lesions (Stelzmann et al., 1995), the two main hallmarks of AD, extracellular amyloid-β (Aβ) plaques and intraneuronal aggregates of hyperphosphorylated tau protein, so-called neurofibrillary tangles. Aβ is released from the amyloid precursor protein (APP) by cleavage of β- and γ-secretases (Haass, 2004) and accumulates in the extracellular space of the brain to diffuse or dense-core plaques (Serrano-Pozo et al., 2011). Intravital imaging studies of APP transgenic mice confirmed that smaller dense-core plaques can cluster together, thus forming lager plaques (McCarter et al., 2013) that are associated with neuronal and synapse loss (Tsai et al., 2004; Spires et al., 2005), increased neurite curvature (Garcia-Alloza et al., 2006; Meyer-Luehmann et al., 2008), impaired neuronal activity in dendritic segments...
Polymerization, where monomers form dimers, oligomers, and the accumulation of glial cells (Bolmont et al., 2008; Meyer-Luehmann et al., 2008; Kuchibhotla et al., 2009; Delekate et al., 2014). However, memory impairments and cognitive decline are most likely caused by synapse dysfunction and synapse loss rather than due to mere neuronal loss or the accumulation of Aβ plaques and neurofibrillary tangles (Terry et al., 1991; Masliah et al., 1994; Koffie et al., 2011). Electron microscopy and immunohistochemical stainings for synaptic markers revealed significant reductions in synaptic density in the cortex and hippocampus (Scheff et al., 1990; Terry et al., 1991; Masliah, 2001). Although the cause of synapse loss has not yet been fully elucidated, most likely both lesions, Aβ and tau, contribute to neurodegeneration.

Besides aging, new genetic risk factors for AD were reported recently in GWAS, such as Apol/Clusterin, PICALM, complement receptor 1 (CR1), TREM2 and sialic-binding immunoglobulin (ig)-like lectin CD33 (Lambert et al., 2009; Naj et al., 2011; Hollingworth et al., 2012; Guerreiro et al., 2013; Jonsson et al., 2013). Interestingly, some of these genes are involved in Aβ production or clearance (Harold et al., 2009; Lambert et al., 2009), or are part of immune-related pathways. During development, synapse elimination was shown to be dependent on microglia phagocytosis that was mediated by C1q and C3 (Stevens et al., 2007). Recently, it was also demonstrated that in young pre-depositing hAPP mice this “developmental synaptic pruning pathway” is activated and leads to synapse loss (Hong et al., 2016).

Aβ plaque formation follows a nucleation-dependent polymerization, where monomers form dimers, oligomers, protofibrils and amyloid fibrils (Harper and Lanser, 1997; Kumar and Walter, 2011). Aβ peptides are 36–43 amino acids in length, whereas Aβ42 is the most neurotoxic fragment, with the highest affinity to aggregate and represents the main component of senile Aβ plaques. Soluble Aβ oligomers are the most neurotoxic species that have been shown to impair long-term potentiation (LTP) (Walsh et al., 2002; Shankar et al., 2008) and enhance long-term depression (LTD) (Li et al., 2009), resulting in weakening of synapses. LTP has been related to the formation of new dendritic spines, increases of postsynaptic densities and the enlargement of spine heads (Maletic-Savatic et al., 1999; Nägerl et al., 2004). In contrast, LTD has been shown to increase structural plasticity (Spires et al., 2005), whereas increased spine density and synaptic markers were obtained upon the removal of soluble oligomers (Spires-Jones et al., 2009). Together, these results support the idea that soluble forms of Aβ are toxic to synapses.

In mouse models of AD, synapse loss is primarily found around dense-core Aβ plaques (Koffie et al., 2009), whereas no synapses are lost in the vicinity of diffuse plaques (Masliah et al., 1990), thus indicating that dense-core Aβ plaques release toxic soluble Aβ oligomers into the surrounding tissue (Takahashi et al., 2004; Koffie et al., 2009), leading first to synaptic dysfunction and finally to complete synapse loss. In several mouse models of AD, synapse numbers are significantly decreased compared to non-transgenic control mice already at pre-depositing stages (Hsia et al., 1999; Mucke et al., 2000; Shankar et al., 2009; Harris et al., 2010).

The role of tau in synapse loss is less well established. During the course of AD tau tangle formation and synapse loss in human AD brains and in mouse models of tauopathy, tangle bearing neurons comprise fewer synapses onto their somata and express less synaptic proteins compared to healthy neurons (Callahan et al., 1999; Ginsberg et al., 2000). The overexpression of mutant P301L in rTg4510 mice led to altered synaptic function and synapse loss (Crimins et al., 2011).

**GLIAL CELLS**

Neuronal synapse formation is based on the interplay between neurons and glial cells. Microglia, the immune cells of the brain parenchyma, regulate synapse formation (Parkhurst et al., 2013) and synapse engulfment via the complement system, which is part of the innate immune system (Wu et al., 2015). In contrast, astrocytes provide nutrients to neurons, take up and release neurotransmitters and provide structural support for neurons (Verkhratsky et al., 2010; Clarke and Barres, 2013). Oligodendrocytes are myelin-forming cells guaranteeing a fast movement of action potentials through axons. Recently, a new cell population was defined as oligodendrocyte precursor cells or NG2-glia (Dimou and Gallo, 2015). In the hippocampus synaptic transmission occurs between NG2-glia and axons. Furthermore, NG2-glia can receive direct excitatory and inhibitory synaptic input from neurons mediated by the neurotransmitters glutamate and GABA. However, the functional role of this neuron to glia synapse is not yet entirely understood (Lin and Bergles, 2004; Bergles et al., 2010). The discovery of NG2-neuron synapses offers the possibility to further investigate the relationship between NG2-glia and neurons in the brain. Interestingly, during their differentiation step from NG2-glia to more mature stages (oligodendrocytes), these cells lose their synapses with neurons (De Biase et al., 2010). Due to the dearth of data, we will focus in this review more on the role of microglia and astrocytes and synapse loss.
Microglia

Microglia mediated synapse loss, or synapse pruning is an important physiological process for proper brain maturation during development. Understanding microglia function in healthy conditions can further help to get insights into their contribution to synapse loss and dysfunction early in disease. Microglia constantly extend and retract their processes and scan their local environment, thereby exploring the entire brain volume (Nimmerjahn et al., 2005). Several studies confirmed that microglia directly contact synaptic elements, thus affecting many synapses (Tremblay et al., 2010; Paolicelli et al., 2011; Schafer et al., 2012). Recent work has also shown that disruption of microglia function resulted in deficient synaptic pruning that was associated with weak synaptic transmission leading to functional connectivity deficits (Paolicelli et al., 2011; Zhan et al., 2014). Furthermore, this microglia-mediated synaptic elimination was shown to be dependent on neuronal activity (Schafer et al., 2012). In addition, depletion of microglia led to a reduction in motor-learning-dependent synapse formation (Parkhurst et al., 2013), implicating microglia in sculpting synaptic connectivity.

Aβ plaques in human AD brains and in mouse models of AD are surrounded by microglia (Meyer-Luehmann et al., 2008; Serrano-Pozo et al., 2013) with impaired process extension (Figure 1A). Microglia cells can be classified into three main types based on their morphology: ramified, hypertrophic and amoeboid. Ramified microglia are found in plaque-free areas of the brain, whereas hypertrophic and amoeboid microglia with short, thick and poorly ramified processes are typically associated with senile plaques (Brawek et al., 2014). Interestingly, microglia are not only the resident monocytes in the brain but are also present in the retina, where Aβ deposits have been reported as well in AD patients and AD mice (Ning et al., 2008; Grimaldi et al., 2018). Similar to the brain, the retina of late-symptomatic AD mice contains less ramified microglia when compared to wildtype (WT) controls (Grimaldi et al., 2018). Recently, with the help of advanced technologies, more microglial phenotypes have been described. By comparing microglia cells from WT and 5xFAD transgenic mice using single-cell RNA-sequencing, disease associated microglia (DAM) co-localizing with Aβ plaques were identified (Keren-Shaul et al., 2017). Though, their precise role in synapse clearance and remodeling requires further investigation (Deczkowska et al., 2018). Moreover, an electron microscopy study defined “dark” microglia that are under stead state conditions rarely present but become prevalent in mouse models with AD pathology. Those “dark” microglia are predominantly active at synapses with condensed, electron-dense cytoplasm and nucleoplasm (Bisht et al., 2016). Ultimately, another study depicted the switch of microglia from a homeostatic to a neurodegenerative phenotype by gene expression analyses (Krasemann et al., 2017). However, the exact function of microglia in the context of AD is still not understood. In any case, they play either a beneficial or detrimental role in AD pathology, including the degradation of Aβ or the stimulation of neurotoxicity through inflammatory cytokine release (Wyss-Coray and Rogers, 2012). Several genes expressed or enriched in microglia appeared to be involved in Aβ clearance, including CD33 (Griciuc et al., 2013). Furthermore, members of the classical-complement-cascade, Clusterin and CR1 have been linked to late onset AD (Jun et al., 2010; Fonseca et al., 2016). The best characterized molecules involved in synapse removal by microglia are components of the complement cascade that is upregulated in AD brains. Furthermore, Aβ and tau aggregates can induce microglial and complement activation (Rogers et al., 1992; Shen et al., 2001). A recent study implicates microglia, complement and immune-related pathways as early mediators.
of synaptic dysfunction (Hong et al., 2016). In the hippocampus of AD mice, the complement proteins C1q and C3 were upregulated and connected with synapses at pre-depositing stages, causing extended engulfment of synaptic elements (Hong et al., 2016). Furthermore, inhibition of C1q, C3 and CR3 rescued synapse loss and synaptic dysfunction in young hAPP mice indicating that microglia are involved in early synapse loss in pre-depositing mice. In addition, C1q-deficient mice that were crossed to Tg2576 mice displayed less astrogliosis and Aβ plaques, suggesting a detrimental role of the complement pathway (Fonseca et al., 2004). Together, these data indicate that pathways responsible for synaptic pruning during development are activated in AD that eventually lead to synapse loss (Stephan et al., 2012; Hong et al., 2016). Interestingly, depletion of microglia (30%) in 3xTg AD mice improved cognition but did not alter Aβ plaque load, suggesting that microglia might play a role in cognitive dysfunction independent of Aβ pathology (Dagher et al., 2015). Alternatively, it has been proposed that Aβ binds to postsynaptic glutamatergic receptors leading to synapse inactivation (Decker et al., 2010; Li et al., 2011). Microglia might then be recruited to the Aβ tagged synapse and induce the removal of this complex.

**ASTROCYTES**

Astrocytes represent the most abundant cell type in the brain. They are involved in synapse formation and elimination, synaptic plasticity and activity. Due to their essential role in brain function it is likely that astrocyte dysfunction results in progression of neurodegenerative diseases. Similar to microglia, reactive astrocytes surround senile Aβ plaques in the brain of AD patients and in mouse models of AD. They become reactive as indicated by their hypertrophic processes and increased expression of GFAP (Wisniewski and Wegiel, 1991; Sofroniew, 2009) (Figure 1B). On the one hand, astrocytes are able to degrade and phagocytose Aβ and reduce Aβ mediated neurotoxicity (Wyss-Coray et al., 2003), but on the other hand they induce microglia activation by releasing proinflammatory factors (Wyss-Coray and Rogers, 2012). Vice versa, a subtype of reactive astrocytes (A1) that is abundant in the AD brain, is induced by neuroinflammatory microglia (Liddelow et al., 2017). As AD pathology progresses, reactive astrocytes upregulate the adenosine receptor A2A, thereby leading to long-term memory loss due to affected astrocyte-synapse interactions. In addition, conditional genetic removal of the A2A-receptor enhanced memory function in hAPP mice (Orr et al., 2015). These findings suggest that increased levels of astrocortical A2A receptor due to AD pathology might contribute to memory loss. Moreover, resting Ca²⁺ levels are enhanced in AD mice and frequent Ca²⁺ transients and intracellular Ca²⁺ waves are present, all of which can lead to the release of gliotransmitters (glutamate, ATP, GABA) (Kuchibhotla et al., 2009; Henneberger et al., 2010; Lee et al., 2010; Woo et al., 2012). Furthermore, production of GABA by reactive astrocytes is increased in APPPS1 mice, though inhibition of GABA production or release from reactive astrocytes fully recovers spike probability, synaptic plasticity, learning and memory loss in these mice (Jo et al., 2014).

Further investigations of neuron-glia signaling pathways and their disruption in neurodegenerative diseases are necessary for the development of new successful therapies that are promising due to the early involvement of glia in the disease process.

**THERAPEUTIC APPROACHES**

Although our knowledge regarding the mechanism underlying AD pathogenesis has improved over the last decades, there is still no cure available. Moreover, open questions concerning memory and synapse loss, as well as gliosis and related neuronal damage, still remain (De Strooper and Karran, 2016). Most current therapeutic approaches focused on the reduction of Aβ levels and Aβ plaque load by inhibiting or modifying the generation of Aβ. Other attempts tried to target the tau protein instead (Roberson et al., 2007; Ittner et al., 2010). The reduction of endogenous WT murine tau by 50% circumvented synaptic and behavioral deficits in hAPP mice, without affecting Aβ plaque load (Roberson et al., 2007). Although the mechanism by which Aβ-mediated cognitive deficits are prevented without diminishing Aβ levels remains elusive. In vivo imaging of 3xTg-AD mice revealed spine loss on dystrophic dendrites positive for hyperphosphorylated tau in areas without plaques (Bittner et al., 2010). Further investigations on the function of tau in mouse models of AD will provide insights regarding the role of tau in AD.

Prime targets for AD therapies are β- and γ-secretase inhibitors. Numerous inhibitors currently undergo clinical trials (May et al., 2011; Lucas et al., 2012; Wang et al., 2014; Yan and Vassar, 2014). Therefore, several studies have tested β- and γ-secretase inhibitors in mouse models of AD. In vivo 2-photon imaging allows to explore structural plasticity of synapses in living mice, even for long-time periods (Grunzendorl et al., 2002; Tsai et al., 2004; Spires et al., 2005; Fuhrmann et al., 2007; Liebscher and Meyer-Luehmann, 2012; Liebscher et al., 2014) and the effect of administered drugs on the plasticity of spines and synapses can be directly monitored. Two different γ-secretase inhibitors, DAPT and LY450139, were tested in WT and APP-KO mice on structural plasticity of dendritic spines. Bittner et al. (2009) could show that APP-KO mice have an increased spine density and that γ-secretase inhibition reduces the number of spines in an APP-dependent manner. Other studies performed in vivo 2-photon imaging and followed dendritic spines and axonal boutons over the course of several weeks in APPS1 mice. Pre- and postsynaptic structures showed an enhanced instability in the vicinity of Aβ plaques (Grunzendorl and Gan, 2007; Spires-Jones et al., 2007; Liebscher et al., 2014). Four weeks treatment with a γ-secretase inhibitor (ELN594) efficiently reduced Aβ plaque formation and growth and stabilized spines near plaques (Liebscher et al., 2014).

Unfortunately, the inhibition of BACE1 is known for its mechanism-based side-effects. Conditional deletion of BACE1 in 5xFAD mice resulted in reduced Aβ plaque load and improved synaptic function, determined by LTP and contextual fear conditioning experiments (Hu et al., 2018). However, ablation
of BACE1 in mice is not without issues, as those mice exhibit abnormal astrogenesis, neurogenesis, hyperactivities, impaired axonal growth and altered LTP (Vassar, 2014). Pharmacological inhibition of BACE1 slowed down plaque formation and reduced dendritic spine formation via Seizure Protein 6 in long-term in vivo imaging experiments (Filsler et al., 2015; Peters et al., 2018; Zhu et al., 2018). Further studies are needed to elucidate how side-effects can be reduced to a minimum e.g., by partial inhibition of BACE1 (Fukumoto et al., 2002; Zhao et al., 2007).

The oligomeric form of Aβ is often considered as the toxic form. Immuno therapy against Aβ oligomers had little effect on synapse loss in the vicinity of Aβ plaques but abolished synapse loss further away from plaques (Dorostkar et al., 2014), suggesting that synapse loss is not primarily mediated by oligomers. In another study, switching off oligomer production resulted in improved cognitive and synaptic impairment (Fowler et al., 2014). However, despite these promising results in preclinical studies, removing toxic Aβ species from the brain with active immunization failed in clinical trials (Hyman, 2011).

To date, it remains an open question whether such Aβ lowering strategies will be successful. Therefore, alternative treatment options should be considered. Mice exposed to an environmental enrichment developed enhanced numbers of new dendritic spines, excitatory synapses and dendritic branches on pyramidal neurons (Mora et al., 2007). Environmental enrichment has also been shown to ameliorate Aβ plaque load, synapse loss and impaired synaptic plasticity (Lazarov et al., 2005; Cracchiolo et al., 2007; Herring et al., 2009; Ziegler-Waldkirch et al., 2018a,b). In a non-pharmacological approach, housing in an environmental enrichment reduced Aβ plaque load by activating phagocytic microglia in 5xPADD transgenic mice (Ziegler-Waldkirch et al., 2018a). Furthermore, adult neurogenesis was revived and cognitive deficits caused by induced Aβ plaque deposits were rescued (Ziegler-Waldkirch et al., 2018a). Future research on the microglia function and dysfunction in CNS disorders, such as pruning, regulating plasticity and neurogenesis will undoubtedly play a predominant role in the search for an effective cure.

CONCLUSION

Besides the physical degeneration of synapses in AD and other neurodegenerative diseases, it is unclear which role glial cells play during the process of synapse loss. Further research will hopefully provide more insights into the role of glial cells and their contribution to synapse loss, in particular at earlier pre-depositing stages when synapses are already vulnerable. Future preclinical treatment approaches should combine pharmacological, non-pharmacological and behavioral studies.

AUTHOR CONTRIBUTIONS

SZ-W and MM-L contributed equally to this work, wrote the manuscript, read and approved the final manuscript.

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receptor-dependent mechanism that is mediated by glycogen synthase kinase 3β in primary cultured hippocampal neurons. J. Neurosci. 30, 9166–9171. doi: 10.1523/JNEUROSCI.1074-10.2010

Deczkowska, A., Kerem-Shaul, H., Weiner, A., Colonna, M., Schwartz, M., and Amit, I. (2018). Disease-associated microglia: a universal immune sensor of neurodegeneration. Cell 173, 1073–1081. doi: 10.1016/j.cell.2018.05.003

Delekate, A., Füchtemeier, M., Schumacher, T., Ulbrich, C., Foddis, M., and Petzold, G. C. (2014). Metabotropic P2Y1 receptor signalling mediates astrocytic hyperactivity in vivo in an Alzheimer’s disease mouse model. Nat. Commun. 5:5422. doi: 10.1038/ncomms6422

Dimou, L., and Gallo, V. (2015). NG2-glia and their functions in the central nervous system. Glia 63, 1429–1451. doi: 10.1002/glia.22859

Dorostkar, M. M., Burgold, S., Filser, S., Barghorn, S., Schmidt, B., Anumala, U. R., Delekate, A., Füchtemeier, M., Schumacher, T., Ulbrich, C., Foddis, M., and Dimou, L., and Gallo, V. (2015). NG2-glia and their functions in the central nervous system. Glia 63, 1429–1451. doi: 10.1002/glia.22859

Dudai, Y., and Morris, R. G. M. (2013). Memorable trends.

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of dysfunctional microglia in neurodegenerative diseases. *Immunity* 47, 566.e9–581.e9. doi: 10.1016/j.immuni.2017.08.008

Kuchibhotla, K. V., Lattarulo, C. R., Hyman, B. T., and Backsi, B. J. (2009). Synchronous hyperactivity and intercellular calcium waves in astrocytes in Alzheimer's disease. *Science* 323, 1211–1215. doi: 10.1126/science.1169969

Kumar, S., and Vahl, H. (2011). Phosphorylation of amyloid β (Aβ) peptides—a trigger for formation of toxic aggregates in Alzheimer's disease. *Aging* 3, 803–812. doi: 10.18632/aging.100362

Lambert, J.-C., Heath, S., Even, G., Campion, D., Sleegers, K., Hiltunen, M., et al. (2009). Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. *Nat. Genet.* 41, 1094–1099. doi: 10.1038/ng.439

Lazarov, O., Robinson, J., Tang, Y.-P., Hairston, I. S., Korade-Mirnics, Z., Lee, V.-M.-Y., et al. (2005). Environmental enrichment reduces Aβ levels and amyloid deposition in transgenic mice. *Cell* 120, 701–713. doi: 10.1016/j.cell.2005.11.015

Lee, S., Yoon, B.-E., Berglund, K., Oh, S.-J., Park, H., Shin, H.-S., et al. (2010). Channel-mediated tonic GABA release from glia. *Science* 330, 790–796. doi: 10.1126/science.1184334

Lesnè, S., Koh, M. T., Kotilinè, L., Kayed, R., Glabe, C. G., Yang, A., et al. (2006). A specific amyloid-β protein assembly in the brain impairs memory. *Nature* 440, 352–357. doi: 10.1038/nature04533

Li, S., Hong, S., Sheppardson, N. E., Walsh, D. M., Shankar, G. M., and Selkoe, D. J. (2009). Soluble oligomers of amyloid β protein facilitate hippocampal long-term depression by disrupting neuronal glutamate uptake. *Neuron* 62, 784–801. doi: 10.1016/j.neuron.2009.05.012

Li, S., Jin, M., Koeglsperger, T., Sheppardson, N. E., Shankar, G. M., and Selkoe, D. J. (2011). Soluble Aβ oligomers inhibit long-term potentiation through a mechanism involving excessive activation of extrasynaptic NR2B-containing NMDA receptors. *J. Neurosci.* 31, 6627–6638. doi: 10.1523/JNEUROSCI.0203-11.2011

Liddelow, S. A., Guttenplan, K. A., Clarke, L. E., Bennett, F. C., Bohlen, C. J., Maletic-Savatic, M., Malinow, R., and Svoboda, K. (1999). Rapid dendritic protein facilitate hippocampal neurons. *Science* 283, 1211–1215. doi: 10.1126/science.1169096

Liddelow, S. A., Guttenplan, K. A., Marek, K. A., and Svoboda, K. (2013). Synchronous hyperactivity and intercellular calcium waves in astrocytes in a mouse model of Alzheimer's disease. *Brain Res. Rev.* 55, 78–88. doi: 10.1016/j.brainresrev.2007.03.011

Mora, F., Segovia, G., and del Arco, A. (2007). Aging, plasticity and environmental enrichment: structural changes and neurotransmitter dynamics in several areas of the brain. *Brain Res. Rev.* 55, 78–88. doi: 10.1016/j.brainresrev.2007.03.011

Mucke, L., Masliah, E., Yu, G.-Q., Mallory, M., Rockenstein, E. M., Tatsuno, G., et al. (2000). High-level neuronal expression of α-synuclein in wild-type human amyloid protein precursor transgenic mice: synaptotoxicity without plaque formation. *J. Neurosci.* 20, 4050–4058. doi: 10.1523/JNEUROSCI.20-11-04050.2000

Nägerl, U. V., Eberhorn, N., Cambridge, S. B., and Bonhoeffer, T. (2004). Bidirectional activity-dependent morphological plasticity in hippocampal neurons. *Neuron* 44, 759–767. doi: 10.1016/j.neuron.2004.11.016

Naj, A. C., Jun, G., Beecham, G. W., Wang, L.-S., Vardarajan, B. N., Buros, J., et al. (2011). Common variants at MS4A4A/MS4A6E, CD2AP, CD3 and EPHA1 are associated with late-onset Alzheimer's disease. *Nat. Genet.* 43, 436–441. doi: 10.1038/ng.801

Nimmerjahn, A., Kirchhoff, F., and Helmchen, F. (2005). Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. *Science* 308, 1314–1318. doi: 10.1126/science.1110467

Ning, A., Cui, J., To, E., Ashe, K. H., and Matsubara, J. (2008). Amyloid-β deposits lead to retinal degeneration in a mouse model of Alzheimer's disease. *Invest. Ophthalmol. Vis. Sci.* 49, 5136–5143. doi: 10.1167/iovs.08.068

Orr, A. G., Hsiao, E. C., Wang, M. M., Ho, K., Kim, D. H., Wang, X., et al. (2015). Astrocytic adenosine receptor A2A and G<sub>C</sub>-coupled signaling regulate memory. *Nat. Neurosci.* 18, 423–434. doi: 10.1038/nn.3930

Paolicelli, R. C., Bolosco, G., Pagani, F., Maggi, L., Scannì, M., Panzanelli, P., et al. (2011). Synaptic pruning by microglia is necessary for normal brain development. *Science* 333, 1456–1458. doi: 10.1126/science.1205292

Parkhurst, C. N., Yang, G., Ninan, I., Sasav, J. N., Yates, J. R. III., Lafaille, J. J., et al. (2013). Microglia promote learning-dependent synapse formation through brain-derived neurotrophic factor. *Cell* 155, 1596–1609. doi: 10.1016/j.cell.2013.11.030

Peters, F., Salikhoglu, H., Rodrigues, E., Herzog, E., Blumé, T., Fülscher, S., et al. (2018). BACE1 inhibition more effectively suppresses initiation than progression of β-amyloid pathology. *Acta Neuropathol.* 135, 695–710. doi: 10.1007/s00401-017-1804-9

Prince, M. J. (2015). *World Alzheimer Report 2015: The Global Impact of Dementia*. Available online at: https://www.alz.co.uk/research/world-report-2015 [Accessed on August 29, 2018].

Roberson, E. D., Scarr, B. S., Kписан, A. I., Yan, F., Cheng, I. H., Wu, T., et al. (2007). Reducing endogenous tau ameliorates amyloid β-induced deficits in an Alzheimer's disease mouse model. *Science* 316, 750–754. doi: 10.1126/science.1141736

Rogers, J., Schultz, J., Brachova, L., Lue, L. F., Webster, S., Bradt, B., et al. (1992). Complement activation and β-amyloid-mediated neurotoxicity in Alzheimer’s disease. *Res. Immunol.* 143, 624–630.

Schafer, D. P., Lehrman, E. K., Kautzman, A. G., Koyama, R., Mardindly, A. R., Yamasaki, R., et al. (2012). Microglia sculpt postnatal neural circuits in an activity and complement-dependent manner. *Neuron* 74, 691–705. doi: 10.1016/j.neuron.2012.03.026

Scheff, S. W., DeKosky, S. T., and Price, D. A. (1990). Quantitative assessment of cortical synaptic density in Alzheimer’s disease. *Neurobiol. Aging* 11, 29–37. doi: 10.1016/0197-4580(90)90059-9

Serrano-Pozo, A., Frosch, M. P., Masliah, E., and Hyman, B. T. (2011). Neuropathological alterations in Alzheimer disease. *Cold Spring Harb. Perspect. Med.* 1:a006189. doi: 10.1101/cshperspect.a006189

Serrano-Pozo, A., Muzikansky, A., Gómez-Isla, T., Growdon, H. J., et al. (2012). Differential relationships of reactive astrocytes and microglia to fibrillar amyloid deposits in Alzheimer disease. *J. Neuropathol. Exp. Neurol.* 71, 462–471. doi: 10.1097/nen.0b013e3182333378

Shankar, G. M., Bloodgood, B. L., Townsend, M., Walsh, D. M., Selkoe, D. J., and Sabatini, B. L. (2007). Natural oligomers of the Alzheimer amyloid-β protein induce reversible synaptic loss by modulating an NMDA-type glutamatergic synapse.
