INTRODUCTION

Glial cells are non-neuronal cells that are classified into three major cell types, astrocytes, oligodendrocytes, and microglia, which have different characteristics and functions in the central nervous system (CNS). Astrocytes play essential roles in the regulation of various brain functions. Astrocytes support neuronal survival and metabolism, control blood flow through vasodilation and vasoconstriction, and uptake neurotransmitters and ions at synaptic clefts (Araque et al., 1999, Sofroniew and Vinters, 2010; Hayakawa et al., 2016). Astrocytes also modulate synaptic formation, function and elimination at all stages of development and in adulthood (Allen and Barres, 2005; Stevens et al., 2007; Allen et al., 2012; Chung et al., 2013; Clarke and Barres, 2013; Lopez-Murcia et al., 2015; Lee et al., 2016; Yang et al., 2016a; Terni et al., 2017).

Phagocytosis is an essential element of the innate immune response, which functions as a defense mechanism against pathogens during infection and clearance mechanism for cellular debris produced during normal brain development and injuries (Fricker et al., 2012; Jones et al., 2013). Microglia in the CNS have been regarded as the only major phagocytes that mediate the elimination of synapses, apoptotic cells, neuronal debris, and pathogenic proteins (Tahara et al., 2006; Jana et al., 2008; Meyer-Luehmann et al., 2008; Wang et al., 2015; Pomilio et al., 2016). However, it has been recently shown that astrocytes also have a strong phagocytic capacity and participate in the elimination of synapses and neuronal debris from the brain (Chung et al., 2013; Bellesi et al., 2017). Glial phagocytosis may be directly associated with the prevalence of various neurodegenerative diseases because defects in the phagocytic function of glial cells could result in the accumulation of unwanted elements in the brain with an abnormal immune response. This review discusses recent findings on the phagocytic roles of glial cells in the regulation of normal brain function and speculates on their potential roles in diseased brains.

GLIAL CELLS ARE INVOLVED IN SYNAPSE ELIMINATION VIA PHAGOCYTOSIS

Neurons generate excess synapses during development. These excess synapses subsequently undergo selective elimination to achieve precise neural connectivity (Allen et al., 2012; Clarke and Barres, 2013; Lee et al., 2016). Synapse elimination events also persist in the mature nervous system.
Astrocytes and Microglia mediate synapse elimination by phagocytic pathways. Astrocytes (green) eliminate synapses from neurons (blue) by recognizing “eat-me” signals (red) presented in the unwanted synapses and phagocytosing them through MEGF10 and MERTK receptors (yellow). Astrocytes also mediate synapse elimination indirectly by inducing C1q expression in neurons (blue). C1qtagged synapses can be recognized and eliminated by complement component-3 receptor (C3R, magenta) in microglia (light blue).

MECHANISMS OF MICROGLIA-MEDIATED SYN-APSE ELIMINATION

Microglia are derived from the hematopoietic lineage and express typical pattern recognition receptors. Microglial processes interact with presynaptic boutons and dendritic spines in normal brains, and direct contacts have been observed using electron and two-photon microscopy (Nimmerjahn et al., 2005). Each microglial cell surveys several synapses simultaneously and quickly changes its motility in response to extracellular stimuli.

Notably, microglia play critical roles in shaping the neural circuit connectivity of developing and normal brains. Microglia prune synaptic connections by engulfing pre- and postsynaptic elements in the hippocampus and retinogeniculate system during postnatal development (Paolicelli and Gross, 2011; Schafer et al., 2012).

Unwanted developing synapses in the retinogeniculate system are tagged with complement protein C1q, which is the initiating protein of the classical complement cascade (Stevens et al., 2007). The binding of C1q and opsonization of unwanted synapses trigger a protease cascade, which leads to the deposition of the downstream complement protein C3 (Gasque, 2004). Deposited C3 directly activate C3 receptors on microglia, which trigger elimination via microglial phagocytosis (Stevens et al., 2007) (Fig. 1).

The relevant complement proteins are normally downregulated by adulthood in the brain, but recent studies have revealed that C1q is highly upregulated in aging brains (Stephan et al., 2013) and most neurodegenerative diseases (Hong et al., 2016), where it mediates abnormal synapse elimination (see the next section).

Fig. 1. Astrocytes and Microglia mediate synapse elimination by phagocytic pathways. Astrocytes (green) eliminate synapses from neurons (blue) by recognizing “eat-me” signals (red) presented in the unwanted synapses and phagocytosing them through MEGF10 and MERTK receptors (yellow). Astrocytes also mediate synapse elimination indirectly by inducing C1q expression in neurons (blue). C1qtagged synapses can be recognized and eliminated by complement component-3 receptor (C3R, magenta) in microglia (light blue).
refinement of neural circuits in the developing mouse brain (Chung et al., 2013). Retinal ganglion cells in developing mice deficient in the Mef10 and Merkt pathways exhibit failure in the normal refinement of connections and retain excess functional synapses with their primary targets, which are neurons in the dorsal lateral geniculate nucleus. This finding supports the active participation of astrocytes in the eliminating of live synapses rather than a simple removal of dead synaptic debris. Astrocytes also recognize and preferentially engulf weak synapses instead of strong synapses, and the presence of strong synapses is required to initiate this elimination process (Chung et al., 2013).

Microglia are traditionally thought to be the major glial cells that mediate synapse elimination, but astrocytes play a dominant role in eliminating synapses in the developing dorsal lateral geniculate nucleus. This role is partially due to the large number of astrocytes because astrocytes outnumber microglia 7~10-fold in developing brains. Astrocytes also continuously engulf excitatory and inhibitory synapses throughout the brain during adulthood, which suggests that astrocytes constantly remodel the synaptic architecture of our brains in response to our experiences.

**GLIAL CELLS IN AGING AND NEURODEGENERATIVE DISEASES**

Aging is the major risk factor for neurodegenerative diseases and cognitive decline. Synapse dynamics is the rate of synapse formation and elimination and is significantly altered by aging and changes in glial gene expression. Notably, C1q accumulates in aged brains approximately 300-fold greater compared to younger brains (Fraser et al., 2010; Depboylu et al., 2011; Stephan et al., 2013). This dramatic accumulation of C1q protein likely increases the vulnerability of brains to hyperactivation of the complement cascade, which can damage even healthy synapses via uncontrolled microglial phagocytosis. However, the triggers for the accumulation of C1q protein and microglial hyperactivation in healthy aging brains are not known. Microglia exhibit increased immune responses, including phagocytosis, following various stimuli and aging, but astrocytes appear to lose their phagocytic capacity during reactive astrogliaosis (Hong et al., 2016; Liddelow et al., 2017), which is a common feature of astrocytes in aging brains.

Drosophila glial cells in aged brains also lose their phagocytic capacity because of the decreased translation of draper, which is a homolog of Mef10 that astrocytes use for phagocytosing synapses (Tasdemir-Yilmaz and Freeman, 2014; Pearce et al., 2015; Purice et al., 2016). Restoration of the Draper levels rescue the phagocytic capacity of glial cells, which efficiently clear damaged axonal debris in aged brains to a similar extent as young brains. Taken together, these new findings suggest that aging may alter the phagocytic capacity of glial cells in the mammalian brain and lead to changes in brain and synaptic homeostasis, which may increase the vulnerability of aged brains to develop various neurodegenerative diseases.

**GLIAL CELL PHAGOCYTOSIS IN ALZHEIMER’S DISEASE (AD)**

The release of proinflammatory cytokines by reactive microglia and astrocytes surrounding β-amyloid plaques is one of the leading factor in chronic inflammatory responses in AD (Salminen et al. 2009; McGeer and McGeer, 2013). This neuroinflammation plays a critical role in the pathogenesis of AD via the induction of neuronal toxicity and cognitive decline (Akiyama et al., 2000; Lee et al., 2010). However, reactive gliosis may also be beneficial because reactive microglia and astrocytes are able to phagocytose and clear Aβ deposits (Lee et al., 2010). Microglia mediate the clearance of Aβ through receptor-mediated phagocytosis via the use of advance glycation end products (RAGE), toll-like receptors 2 (TLR2) and 4 (TLR4), scavenger receptor CD36, PS receptor and purine receptor P2Y6 (Noda and Suzumura, 2012; Jones et al., 2013). Microglial uptake of Aβ and its subsequent targeting to the endosome-lysosome pathway were examined in detail using active microglia phagocytosing of monomeric, oligomeric and fibrillar Aβ (Lee and Landreth, 2010). Ultrastructural studies also identified intra-cytoplasmic plastic fragments of Aβ in AD microglia. Microglia are activated and recruited to Aβ deposits in brains that contain neurons that overexpress amyloid precursor protein (APP) (Tahara et al., 2006; Bolmont et al., 2008; Meyer-Luehmann, et al., 2008). Microglia constitutively express TLR2 (Olson and Miller, 2004; Hanke and Kielian, 2011), and TLRs play a role in Aβ-induced microglial activation (Chen et al., 2006; Tahara et al., 2006; Tang et al., 2007; Liu et al., 2012). Aβ-triggered inflammatory activation is reduced in TLR2-deficient microglia (Jana et al., 2008; Suh et al., 2013), and TLR2 deficiency reduces Aβ-triggered inflammatory activation in cultured microglia, which suggests a beneficial effect of TLR2 inhibition in AD pathogenesis (Liu et al., 2012).

Triggering receptors expressed by myeloid cells (TREM) are surface receptors on microglia, and TREM mutations confer a dramatically elevated risk for AD and other neurodegenerative diseases (Cuypers et al., 2014). Microglia highly express TREM2 (Painter et al., 2015), which is a key determinant of the CNS response to Aβ accumulation (Zhang et al., 2013; Matarin et al., 2015; Sikoe and Hardy, 2016). Deletion of the TREM2 allele in human APP (hAPP) transgenic mice decreased the number of microglia associated with Aβ deposits (Ulrich and Holtzman, 2016). Defective mTOR signaling in TREM2-deficient microglia is associated with a compensatory increase in autophagy in vitro and in vivo in AD models (Ul-land et al., 2017). TREM2 detects damage associated with lipids, which enables microglia to sense Aβ accumulation and cell damage and supports microglia survival and Aβ-mediated reactive microgliosis (Wang et al., 2015). A recent study also described a novel microglia type associated with neurodegenerative disease (DAM) in AD model mice. Single cell analysis of DAM revealed that the DAM program was activated in a TREM2-independent and -dependent manner in the two-step activation processes, and disease-related gene expression changes were observed (Keren-Shaul et al., 2017).

AD is associated with profound synapse loss early in the disease state. A recent study demonstrated reactivation of the complement pathway that is downregulated after initial synaptic pruning periods in AD brains and mediates abnormal synapse pruning via microglial cells (Hong et al., 2016). Functional suppression of C1q prevents synapse loss during...
disease progression, which supports the microglial cell mediation of synapse loss in AD brains. Reactive astrocytes also surround the sites of Aβ deposits in human and animal AD models and contribute to AD pathophysiology via the release of proinflammatory cytokines and activation of microglia-mediated cytotoxicity (Jana et al., 2008; Park et al., 2008; Lee et al., 2010; Fu et al., 2014; Painter et al., 2015; Yang et al., 2016b). However, astrocytes are also competent phagocytes, and their ability to engulf Aβ may be important in the identification of strategies to reduce Aβ accumulation in AD (Jones et al., 2013). Few studies have examined the phagocytic roles of astrocytes in Aβ clearance, but a decrease in Aβ levels was reported when astrocytes were added to brain sections prepared from a mouse model of AD (Wyss-coray et al., 2003). Astrocyte transplantsations into the brains of transgenic AD mouse models containing mutated APP and PSEN1 (PS1), APPswe/PS1dE9, were found near Aβ deposit and internalized Aβ. Thus, astrocytes have a capacity of clearance of Aβ (Pihlaja et al., 2008). In addition, astrocytic LRP-1 is reported to mediate Aβ clearance and regulates Aβ metabolism both in vitro and in vivo models (Liu et al., 2017).

The phagocytic roles of astrocytes may also be important in maintaining brain homeostasis. A recent study found that the strongest genetic risk factor for AD, APOE4, suppressed astrocyte-mediated phagocytosis (Chung et al., 2016). By contrast, the protective APOE allele for AD, APOE2, significantly enhanced the phagocytic capacity of astrocytes in vitro and in vivo. C1q protein accumulation, which may represent the amount of senescent synapses with increased vulnerability to complement-mediated degeneration, was also significantly reduced in APOE2 knock-in (KI) animals, and C1q accumulation was significantly increased in APOE4 KI animals in the 18-month-old mouse hippocampus. Astrocytes constantly engulf synapses in adult brains, and the decreased C1q accumulation in aged APOE2 KI animals supports the hypothesis that maintaining the synaptic environment devoid of senescent synapses prevents aberrant immune activation/inflammation and neurodegeneration. By contrast, a decrease in the overall phagocytic capacity of astrocytes may lead to the accumulation of senescent synapses and their debris, which may be at least partially responsible for the enhanced vulnerability of the brain to AD via hyperactivation of the complement pathway (Chung et al., 2016).

GLIAL CELL PHAGOCYTOSIS IN HUNTINGTON’S DISEASE (HD)

HD is an autosomal dominant inherited neurodegenerative disorder. Patients suffering from HD exhibit specific symptoms, such as random involuntary movements as well as psychiatric and cognitive impairment (Jiang et al., 2016; Jansen et al., 2017). These symptoms are highly associated with neuronal dysfunction in the striatum and other brain regions (Ghosh and Tabriz, 2015). HD is caused by an expanded polyglutamine repeat localized to the N-terminal region of the huntingtin protein, with intracellular accumulation and aggregation (Jiang et al., 2016). Astrocytes and microglia are activated in HD patients, as shown by GFAP and Iba1 upregulation (Jansen et al., 2016). Astrocytes with mutant huntingtin (mHTT) downregulate potassium channel Kir4.1, which leads to increased extracellular potassium concentrations and subsequent neuronal excitability (Tong et al., 2014; Sofroniew, 2015). The loss of the Kir4.1- and Glt-1 (Glutamate transporter 1)-mediated homeostatic functions of astrocytes cause defects in astrocytic glutamate and Ca2+ signaling, which contribute to the altered neuronal physiology in the striatum. Defects in the striatal circuit in HD patients are remedied by correcting key astrocyte homeostatic dysfunctions that precede overt astrogliosis and neurodegeneration (Jiang et al., 2016).

mHTT aggregation in drosophila neurons was transported to astrocytes via Draper. This phagocytic clearance of neuronal mHTT aggregation by glial cells may contribute to the spread of pathogenic protein aggregates in various neurodegenerative diseases (Pearce et al., 2015). Although there are a few studies reporting the presence of mHTT inclusions in astrocytes and oligodendrocytes (Shin et al., 2005; Tong et al., 2014; Huang et al., 2015; Jansen et al., 2016), precise molecular mechanisms of this phenomenon and its implications during the initiation and progression of HD remain elusive.

GLIAL PHAGOCYTOSIS IN PARKINSON’S DISEASE (PD)

PD is a progressive neurological disorder that is characterized by the loss of dopaminergic neuron in substantia nigra pars compacta (SNpc), which results in tremor, bradykinnesia, and muscle stiffness. α-synuclein is a major component of the intracelluar protein deposits, called Lewy bodies, in specific regions of the brain stem, spinal cord, and cortex (Park et al., 2008; Lees et al., 2009; Phatnani et al., 2015). Previous studies have demonstrated that α-synuclein influenced microglia activation (Austin et al., 2006; Klegeris et al., 2008). Microglial cells treated with extracellular monomeric α-synuclein exhibited increased phagocytic activity in vitro in time- and dose-dependent manners (Park et al., 2008; Fu et al., 2014). By contrast, aggregated α-synuclein inhibited the phagocytic capacity of microglial cells by antagonizing monomeric-facilitated clearance and decreasing the basal microglial phagocytic capability (Park et al., 2008; Fu et al., 2014). A recent study reported that astrocyte-derived GDNF regulated midbrain microglial microactivation and exhibited a neuroprotective effect via inhibition of the degeneration of dopaminergic neurons in the nigrostriatal system in PD animal models (Rocha et al., 2012). Previous studies also demonstrated that various microglial receptors, including the C1q-mediated clearance pathway (Depboylu et al., 2011) and scavenger receptor class B (Michaelakakis et al., 2012), were involved in the endocytosis of α-synuclein. Several studies have demonstrated that microglia were more effective in endocytosing α-synuclein compared to astrocytes and neurons (Rojanathammanee et al., 2011; Fu et al., 2014), but whether microglial uptake of α-synuclein plays a beneficial or harmful response to the pathophysiology of PD is not clear.

GLIAL PHAGOCYTOSIS IN MOTOR NEURON DISEASES

Amyotrophic lateral sclerosis (ALS) is characterized by a progressive loss of motor neurons in the motor cortex, brainstem, and spinal cord (Hardiman et al., 2011; Radford, 2015). ALS exhibits rapid disease progression and leads to death
mediated phagocytosis play various roles under different physiological conditions. In normal and healthy conditions, glial phagocytosis involves in regulation of neural circuit remodeling by eliminating unwanted synapses and neurites. Furthermore, glia mediates removal of apoptotic cells and neuronal debris in maintaining brain homeostasis. In pathological conditions, astrocytes and microglia phagocytose protein aggregates, such as Aβ, Htt, and α-Syn to clear accumulated proteins in the brains with neurodegenerative diseases. However, hyperactivation of glial phagocytosis can play deleterious roles by phagocytosing and eliminating intact synapses and stressed neurons, contributing to the initiation and progression of neurodegeneration and cognitive declines.

within 2-3 years of symptom onset (Lasiene and Yamanaka, 2011). Astrocytes and microglia are critical regulators via the removal of damaged motor neurons and mutant SOD1 in ALS pathology. Astrocytes become activated and release increased levels of cytokines in ALS, including TNF-α, IFN-γ, and IL-1β (Philips and Robberecht, 2011). Astrocytic protein inclusions containing mSOD1 are an early feature of the disease in the mSOD1 mouse model. Selective expression of mSOD1 in astrocytes alone failed to provoke an ALS phenotype (Gong and Elliott, 2000), but the silencing of mSOD1 expression in astrocytes significantly slowed disease progression in the SOD1G93A mouse model (Yamanaka et al., 2008), without affecting the level of astrogliosis. Previous studies have demonstrated that normal motor neurons develop features of ALS pathology when surrounded by mSOD1-expressing glial cells in chimeric mice models (Clement et al., 2003). Benkler et al. (2013) demonstrated that the reduced glutamatergic response of astrocytes in SOD1G93A mouse models may lead to disruption of glutamate homeostasis and accumulative CNS damage, which facilitate motor neuron degeneration.

Microglia are also a component of ALS pathology. Activated microglia are widely detected in the brains of living ALS patients using positron emission tomography (Turner et al., 2004; Lasiene and Yamakata, 2011). Activation of microglia results in the elevation of proinflammatory cytokines in mutant SOD1 mice. Mutant SOD1-expressing microglia release higher levels of TNF-α and IL-6 compared to wild-type microglia during LPS-induced systemic inflammation produce TNF-α, C1q and IL-1α, which activate astrocytes and microglia to induce the expression of neurotoxins from reactive astrocytes (Liddelow et al., 2017).

Glial cell phagocytosis may play beneficial or deleterious roles in the brain when they are dysregulated. The phagocytic capacity of astrocytes and microglia may be necessary for the clearing of unnecessary synapses, synaptic debris and extracellular protein aggregates, thus maintaining brain homeostasis and preventing aberrant immune responses. In contrast, hyperactivation of phagocytic pathways, such as classical complement cascades and MERTK phagocytic pathways, can induce damage to live synapses during AD (Savage et al., 2015) and neurons during stroke (Neher et al., 2013), respectively.

Further studies would be necessary to reveal the exact molecular and cellular players of the phagocytic events in specific disease settings. This knowledge is crucial to the development of relevant therapeutics targets and strategies for each specific disease.

**ACKNOWLEDGMENTS**

The authors thank all members of Chung’s laboratory for their helpful discussion. This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIP) (NRF-2016M3C7A1905391 and NRF-2016R1C1B3006969) (W.-S.C).
promote formation of excitatory synapses via GluA1 AMPA receptors. Nature 486, 410-414.

Araque, A., Sanzgiri, R. P., Parpura, V. and Haydon, P. G. (1999) Astrocyte-induced modulation of synaptic transmission. Can. J. Physiol. Pharmacol. 77, 699-706.

Austin, S. A., Floden, A. M., Murphy, E. J. and Combs, C. K. (2006) α-synuclein expression modulates microglial activation phenotype. J. Neurosci. 26, 10558-10563.

Bellesi, M., de Vivo, L., Chini, M., Gilli, F., Tononi, G. and Cirelli, C. (2017) Sleep loss promotes astrocytic phagocytosis and microglial activation in mouse cerebral cortex. J. Neurosci. 37, 5263-5273.

Benkler, C., Ben-Zur, T., Barhum, Y. and Offen, D. (2013) Altered as...
nus, T., Camandola, S. and Mattson, M. P. (2007) Pivotal role for neuronal Toll-like receptors in ischemic brain injury and functional deficits. *Proc. Natl. Acad. Sci. U.S.A.* **104**, 13798-13803.

Tasdemir-Yilmaz, O. E. and Freeman, M. R. (2014) Astrocytes engage unique molecular programs to engulf pruned neuronal debris from distinct subsets of neurons. *Genes Dev.* **28**, 20-33.

Teni, B., Lopez-Murcia, F. J. and Llovet, A. (2017) Role of neuron-glia interactions in developmental synapse elimination. *Brain Res. Bull.* **129**, 74-81.

Tong, X., Ao, Y., Faas, G. C., Nwaobi, S. E., Xu, J., Haustein, M. D., Anderson, M. A., Mody, I., Olsen, M. L., Sofroniew, M. V. and Khakh, B. S. (2014) Astrocyte Kir4.1 ion channel deficits contribute to neuronal dysfunction in Huntington’s disease model mice. *Nat. Neurosci.* **17**, 694-703.

Turner, M. R., Cagnin, A., Turkheimer, F. E., Miller, C. C., Shaw, C. E., Brooks, D. J., Leigh, P. N. and Banati, R. B. (2004) Evidence of widespread cerebral microglial activation in amyotrophic lateral sclerosis: an [11C](R)-PK11195 positron emission tomography study. *Neurobiol. Dis.* **15**, 601-609.

Ulland, T. K., Song, W. M., Huang, S. C., Ulrich, J. D., Sergushichev, A., Beatty, W. L., Loboda, A. A., Zhou, Y., Cairns, N. J., Kambal, A., Loginicheva, E., Gilfillan, S., Cella, M., Virgin, H. W., Unanue, E. R., Wang, Y., Artyomov, M. N., Holtzman, D. M. and Colonna, M. (2017) TREM2 maintains microglial metabolic fitness in Alzheimer’s disease. *Cell* **170**, 649-663.e13.

Ulrich, J. D. and Holtzman, D. M. (2016) TREM2 function in Alzheimer’s disease and neurodegeneration. *ACS Chem. Neurosci.* **7**, 420-427.

Wang, Y., Cella, M., Mallinson, K., Ulrich, J. D., Young, K. L., Robinette, M. L., Gilfillan, S., Krishnan, G. M., Sudhakar, S., Zinselmeyer, B. H., Holtzman, D. M., Cirrito, J. R. and Colonna, M. (2015) TREM2 lipid sensing sustains the microglial response in an Alzheimer’s disease model. *Cell* **160**, 1061-1071.

Weydt, P., Yuen, E. C., Ransoom, B. R. and Moller, T. (2004) Increased cytotoxic potential of microglia from ALS-transgenic mice. *Glia* **48**, 179-182.

Wyss-Coray, T., Loike, J. D., Brionne, T. C., Lu, E., Anankov, R., Yan, F., Silverstein, S. C. and Husemann, J. (2003) Adult mouse astrocytes degrade amyloid-β in vitro and in situ. *Nat. Med.* **9**, 453-457.

Yamanaka, K., Chun, S. J., Boilée, S., Fujimori-Tonou, N., Yamashita, H., Gutmann, D. H., Takahashi, R., Misawa, H. and Cleveland, D. W. (2008) Astrocytes as determinants of disease progression in inherited amyotrophic lateral sclerosis. *Nat. Neurosci.* **11**, 251-253.

Yang, J., Yang, H., Liu, Y., Li, X., Qin, L., Lou, H., Duan, S. and Wang, H. (2016a) Astrocytes contribute to synapse elimination via regulated 2′-inositol 1,4,5-trisphosphate receptor-dependent release of ATP. *Elife* **5**, e15043.

Yang, L., Liu, C. C., Zheng, H., Kanekiyo, T., Atagi, Y., Jia, L., Wang, D., N’Songo, A., Can, D., Xu, H., Chen, X. F. and Bu, G. (2016b) LRP1 modulates the microglial immune response via regulation of JNK and NF-κB signaling pathways. *J. Neuroinflammation* **13**, 304.

Zhang, B., Tian, M., Zheng, H., Zhen, Y., Yue, Y., Li, T., Li, S., Marcan- tonio, E. R. and Xie, Z. (2013) Effects of anesthetic isoflurane and desflurane on human cerebrospinal fluid Aβ and t level. *Anesthesiology* **119**, 52-60.

Zhang, Y., Chen, K., Sloan, S. A., Bennett, M. L., Scholze, A. R., O’Keeffe, S., Pithani, H. P., Guarneri, P., Caneda, C., Rudersich, N., Deng, S., Liddelow, S. A., Zhang, C., Daneman, R., Maniatis, T., Barres, B. A. and Wu, J. Q. (2014) An RNA-sequencing transcriptome and splicing database of glia, neurons, and vascular cells of the cerebral cortex. *J. Neurosci.* **34**, 11929-11947.