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The classification of microglial activation phenotypes on neurodegeneration and regeneration in Alzheimer's disease brain

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Abstract

Alzheimer's disease (AD) is a neurodegenerative disease characterized by progressive decline of cognitive function and memory formation. There is no therapeutic that can halt or reverse its progression. Contemporary research suggests that age-dependent neuroinflammatory changes may play a significant role in the decreased neurogenesis and cognitive impairments in AD. The innate immune response is characterized by pro-inflammatory (M1) activation of macrophages and subsequent production of specific cytokines, chemokines, and reactive intermediates, followed by resolution and alternative activation for anti-inflammatory signaling (M2a) and wound healing (M2c). We propose that microglial activation phenotypes are analogous to those of macrophages and that their activation plays a significant role in regulating neurogenesis in the brain. Microglia undergo a switch from an M2- to an M1-skewed activation phenotype during aging. This review will assess the neuroimmunological studies that led to characterization of the different microglial activation states using AD mouse models. It will also discuss the roles of microglial activation on neurogenesis in AD and propose anti-inflammatory molecules as exciting therapeutic targets for research. Molecules like interleukin-4 and CD200 have proven to be important anti-inflammatory molecules in the regulation of neuroinflammation in the brain, and they will be discussed in detail for their therapeutic potential.

Keywords

Alzheimer's disease; microglia; neurogenesis; neuroinflammation

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1. Introduction

Alzheimer's disease (AD) is the most prevalent neurodegenerative disease, and it is characterized by progressive decline of cognitive function and memory formation in mostly elderly populations (Minati et al., 2009). While the exact pathophysiology of AD has yet to be determined, it is known that the greatest risk factor for development of the disease is age. AD presents with a very characteristic neuropathology: intraneuronal accumulations of hyperphosphorylated microtuble-associated protein tau known as neurofibrillary tangles (NFTs), and extracellular deposition of amyloid β-peptide (Aβ) known as amyloid or senile plaques (Dickson et al., 1988; Alzheimer et al., 1995). AD patients also exhibit a significant loss of synapses and neurons, namely in the temporal and frontal cortices and hippocampi (Davies et al., 1987; Scheff et al., 2006; Scheff et al., 2007). Increasing evidence suggests that it is the aggregation of Aβ fragments that causes neurotoxic effects that lead to the neural, synaptic, and cognitive degradation seen in AD, making Aβ the target of most AD research today (Hardy and Selkoe, 2002).

2. APP and Aβ biology

Aβ is formed by the proteolytic cleavage of amyloid precursor protein (APP) (Zhao et al.), a protein that contains an Aβ-encoding region. As APP is secreted from the cell, it undergoes two consecutive proteolytic cleavages by a series of secretases: α then γ, or β then γ (Esch et al., 1990). Members of the ADAM (a disintegrin and metalloproteinase) family have α-secretase activity and are implicated in APP cleavage (Zhang et al., 2011), but because α-secretase cleaves within the Aβ encoding region, it is not a factor in Aβ formation. β-site APP converting enzyme (BACE) 1 and 2 are β-secretases, and both have been implicated as major factors in the formation of Aβ (Vassar et al., 1999). The γ-secretase complex consists of four components: presenilin 1 or 2 (PS1, PS2, the catalytic domains), Nicastrin, APH-1, and presenilin enhancer-2 (PEN-2) (Kimberly et al., 2003; Takasugi et al., 2003). Missense mutations within the PS1 and PS2 genes are the most common cause of early onset familial AD (Levy-Lahad et al., 1995; Sherrington et al., 1995), but mutations in APP have also been seen in more elderly familial cases (Citron et al., 1992). In addition to cleaving APP, γ-secretase also cleaves a large number of transmembrane proteins, including Notch (Haass and De Strooper, 1999), whose cleaved intracellular domain plays an important role as a transcriptional factor in regulating genes involved in development (Kopan et al., 1996; Schroeter et al., 1998).

For non-amyloidogenic cleavage of APP, α-secretase cleaves the protein between amino acid residues 16 and 17 within the Aβ region, creating a short 83-residue fragment known as p83 (Esch, et al. 1990). The p83 fragment is subsequently cleaved by γ-secretase within the transmembrane region, generating p3 (Aβ17-40) and APP intracellular domain (AICD). AICD can potentially translocate to the nucleus and function as a transcription factor Cao and Sudhof (2001); (Baek et al., 2002; Leissring et al., 2002; Cao and Sudhof, 2004). The Aβ fragment is created by cleavage with β- then γ-secretases (Seubert et al., 1993). β-secretase cleaves at the N-terminus of the Aβ region and is followed by cleavage by γ-secretase to create a 40-42-residue Aβ, with the majority of Aβ fragments being Aβ40, and the less common, more amyloidogenic species being Aβ42. Studies of Aβ deposition in

Down Syndrome and biochemical studies of both Aβ40 and Aβ42 have shown that the Aβ42 fragment tends to aggregate into fibrils more readily than the Aβ40 fragment, causing a gradual increase of Aβ42 deposition with age (Jarrett et al., 1993; Iwatsubo et al., 1995; Lemere et al., 1996).

A large number of studies have proven that Aβ has a neurotoxic effect when aggregated in specific forms (Lambert et al., 1998; Hardy and Selkoe, 2002; Walsh et al., 2002). Its formation and build-up precedes the accumulation of hyperphosphorylated tau into NFTs and leads to synaptic dysfunction and neuronal loss (Selkoe, 1991; Mattson et al., 1998; Lue et al., 1999; Shankar and Walsh, 2009). These findings, together with the fact that select familial AD is due to causative gene mutations in the coding sequences of APP, PS1 and PS2, which are directly involved in Aβ formation, led to the development of the "Amyloid Cascade Hypothesis" first proposed by Selkoe in 1996 (Selkoe, 1996). The Amyloid Cascade Hypothesis states that abnormal processing of APP, whether genetic or spontaneous, causes overproduction of Aβ42 fragments. The brain is unable to clear the Aβ, and it gradually accumulates within the brain. The Aβ aggregates are toxic to neurons and synapses, and this leads to innate immune activation of microglia and astrocytes and attendant inflammatory processes, although the exact pathophysiology of this step is largely unknown (McGeer and McGeer, 2010). There is subsequent production and build-up of reactive intermediates and oxygen species that lead to oxidative injury (Kish et al., 1992; Gutowicz, 2011). Other changes in kinase and phosphatase activities lead to the formation of NFTs (Iqbal et al., 1998). These combined toxic effects are thought to be the underlying cause of neuronal loss, synaptic dysfunction, and the subsequent degradation of cognitive function in AD, and this is currently the most widely accepted hypothesis.

The Amyloid Cascade Hypothesis, however, cannot completely explain the degradation in AD based on several pieces of evidence (Struble et al., 2010). Firstly, therapeutics against Aβ, though successful in removing Aβ fragments in animal models and humans, do not stop the progression of AD, meaning it is not the single cause of dementia (Holmes et al., 2008; Salloway et al., 2009). Secondly, Aβ is normally found even in the healthy human brain and in normal cell culture of healthy humans and other mammals (Seubert et al., 1992; Shoji et al., 1992; Haass and De Strooper, 1999), and those individuals with APP or γ-secretase mutations that have higher deposits of Aβ do not show dementia until they are 20-40 years old (Bird, 2008). In fact, about 20-30% of individuals with normal cognition who never develop dementia show significant levels of amyloid burden in the brain (Bennett et al., 2006; Aizenstein et al., 2008). This has led research to aim for the discovery of the other underlying factor(s) that leads to the cognitive decline in AD.

3. Neuroinflammation

It has long been known that inflammation is a prominent factor, not just in AD, but in a number of age-associated diseases, including atherosclerosis, diabetes, rheumatoid arthritis, and multiple sclerosis (MS). In fact, data from transcriptome analyses of brain tissue from normally aging humans and mice showed significant up-regulation of certain genes that occurred with age, and about half of those genes were associated with inflammation and oxidative stress (Prolla, 2002; Lu et al., 2004; Loerch et al., 2008; Bishop et al., 2010). This

can be partly corrected by caloric restriction (Lee et al., 2000), which suggests that energy expenditure-associated oxidative stress underlies the M1 to M2 conversion in the brain. The outcome of oxidative stress can be DNA damage and reduced repair (Haigis and Yankner, 2010). Highly conserved insulin/IGF-1, TOR, and sirtuin signaling pathways regulate these cellular responses, and the aging process potentially induces their dysregulation, leading to pro-inflammatory microglial activation.

Several pieces of evidence indicate the increased presence of inflammatory molecules in AD, including some of the following: the presence of elevated levels of pro-inflammatory cytokines like tumor necrosis factor-α (TNF-α) in the serum of AD patients (Fillit et al., 1991) and interleukin (IL) -6 in brain tissue (Bauer et al., 1991; Bauer et al., 1992) compared to age-matched controls; the increase of activated microglial cells surrounding senile plaques in the cerebral cortex (Haga et al., 1989); the localization of Aβ deposits to T cells, activated microglia, and reactive astrocytes in AD brains (Wegiel and Wisniewski, 1990; Wisniewski and Wegiel, 1991; Ishii and Haga, 1992); and of particular interest in this article is the down-regulated expression of a neuroimmune regulatory protein, cluster of differentiation 200 (CD200), seen in post-mortem brains of AD patients (Walker et al., 2009).

These findings provide evidence for the new hypothesis that the neuronal damage seen in AD is not simply due to the Aβ deposition or intracellular tau accumulation, but to the brain's dysregulated inflammatory and oxidative responses to them (McGeer et al., 1989; McGeer et al., 1994). Indeed, some of the people with increased Aβ load did not develop AD, suggesting that a second factor is necessary for the disease development, such as microgliosis. Using two carbon 11 ([^{11}C])-labeled positron emission tomographic imaging agents, Pittsburgh Compound B (PIB, an Aβ marker) and PK-11195 (a benzodiazepine receptor ligand and a microglial marker), several groups examined if PIB and PK11195 binding correlated with cognitive function of AD patients. Two studies reported a negative correlation of cognitive function with microgliosis (PK-11195) but not with Aβ load (PIB) (Edison et al., 2008; Yokokura et al., 2011). However, another small-scale study showed no correlation of PK-11195 binding with clinical diagnosis (Wiley et al., 2009). Other studies showed that, although PIB binding was positively correlated with astrogliosis, it was largely independent from PK-11195 binding (Okello et al., 2009; Kadir et al., 2011). These studies suggest that Aβ load is directly correlated with astrogliosis but not with microgliosis, and therefore, microgliosis is potentially more associated with the cognitive decline in AD.

Of particular interest is the role of the microglial activation switch from the alternative to classical activation phenotype. This change in microglial activation skewing phenotype may be the cause of significant amounts of cortical and hippocampal atrophy that makes neurogenesis a prime target for studying ways to replenish that loss (Volobouéva and Giffard, 2011). This in turn draws attention to the increasing significance of the role of immunomodulatory molecules, such as CD200, in neuroimmune regulation. This review will go over the innate and adaptive immune systems of the brain and the role of classically or alternatively activated microglia, which lead into the possible mechanisms by which neurogenesis can be restored in those areas most affected by neuroinflammation. Lastly, this review will discuss the role of CD200 in immune homeostasis and how it may be used to

reverse neuroinflammation based on neuroimmunological studies of AD mouse models and AD patients.

4. The Innate and Adaptive Immune Responses

The immune response of the central nervous system (CNS) follows a well-characterized signaling pathway in response to tissue injury, cell death, and pathogens (Carpentier and Palmer, 2009). The main cells that direct the innate immune response in the CNS are mononuclear phagocytes (brain resident microglia and perivascular macrophages). These cells function as sentinels in the brain and prominently express pathogen recognition receptors (PRRs) that recognize the signaling pathways activated or released by dying or damaged cells known as pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). PRRs include Toll-like receptors (TLRs), Nucleotide Oligomerization Domain (NOD)-like receptors (NLRs), and Retinoic acid-Inducible Gene 1 (RIG1)-like receptors (RLRs). TLRs are ubiquitously expressed and are often expressed on the plasma membranes of immune cells and glial cells, including microglia, astrocytes, and neurons (Bsibsi et al., 2002; Tang et al., 2007). Interestingly, Aβ itself also acts as a PAMP molecule and interacts with TLRs (Lotz et al., 2005; Reed-Geaghan et al., 2009). NLRs are found in the cytoplasm, and some NOD ligands, such as muramyl dipeptide (MDP), are also expressed in microglia, astrocytes, and neurons, and they have been shown to activate the neuronal cells *in vitro* (Chauhan et al., 2009; Li et al., 2010). When stimulated by a ligand, such as lipopolysaccharide (LPS, a TLR ligand) or MDP, TLRs or NLRs become activated and initiate transcriptional up-regulation and release of pro-inflammatory cytokines and chemokines (Bailey et al., 2006). This LPS-induced inflammatory response is enhanced in aged animals *in vivo* (Sparkman and Johnson, 2008; Lynch, 2010). The cytokines released include pro-inflammatory cytokines, such as TNF-α, interferon-γ (IFN-γ), IL-6, and IL-1β. The cytokines initiate the adaptive immune response, activate vasculature, and recruit circulating lymphocytes to the infection or injury. The lymphocytes bind to the activated endothelium and diffuse throughout the affected tissue. Through antigen recognition and with the help of B-cell-mediated antibody production, they remove pathogens by T-cell-mediated destruction of cells. Following the elimination of pathogens, the immune response self-limits itself by the clearance of the molecular patterns that initially triggered the immune response and by Fas ligand (FasL)-mediated apoptosis of activated T cells (Niederkorn, 2006). Both T and B cells undergo apoptosis. The hypothalamo-pituitary-adrenal (HPA) axis is activated during inflammation and increases the production of glucocorticoids to conversely decrease pro-inflammatory signaling. Perivascular macrophages are essential for the anti-inflammatory HPA response to IL-1 (Serrats et al., 2010). Without them, CNS responses to inflammatory insults are enhanced. These cells induce the HPA axis and constrain endothelial cell involvement in prostanoid production during the response to pro-inflammatory signals (Serrats et al., 2010). With the help of lymphocytes, microglia, and neurons, the HPA axis also contributes to the production of anti-inflammatory hormones and cytokines such as IL-4, IL-10, and transforming growth factor-β (TGF-β) (Elenkov and Chrousos, 2002). With that, the immune signaling cascade is resolved and returned to its previous state of surveillance of the CNS.

5. Classification of Macrophage Activation – M1/M2 Switch of activation phenotype

5.1. Classical (M1) Activation

Macrophages are a type of white blood cell derived from monocytes that aid in the removal of foreign substances or organisms by phagocytosis (Mackaness, 1970; David, 1975; Oppenheim and Rosenstreich, 1976). Macrophage activation is classified into two phenotypes: classical and alternative (Mills et al., 2000; Gordon, 2003). Classical activation involves the induction of M1 macrophages by Th1 cell-derived cytokines, like IFN-γ, TNF-α, and IL-1β, to allow cells to respond to PAMPs. M1 macrophages express opsonic receptors, such as immunoglobulin Fc γ receptors (e.g. FcγRIII) (Unkeless et al., 1988; Ravetch and Kinet, 1991). Their activation causes the cells to release high levels of pro-inflammatory cytokines, including TNF-α, STAT3, IL-6, IL-12, IL-1β, and IL-23, nitric oxide synthase (NOS), NADPH oxidases (NOX), and corresponding toxic intermediates, and reactive oxygen and nitrogen species (Gutteridge and Halliwell, 1989; Heinrich et al., 1998; Akiyama et al., 2000; Pratico et al., 2001; Pratico and Sung, 2004; Brown, 2007; Benoit et al., 2008; Burton et al., 2011). Conversely, they have low production of anti-inflammatory cytokines. LPS is known to stimulate M1 activation via the TLR4 complex, which then triggers an intracellular signaling cascade that activates NFκB and three types of mitogen-activated protein kinases (MAPKs): extracellular signal-related kinase (Erk), c-Jun N-terminal kinase (JNK), and p38 (Nagai et al., 2002; Takeda and Akira, 2004). Without some sort of modulation, as from negative feedback, these defense processes could be over-stimulated and cause significant damage. Inflammatory cytokines and reactive oxygen and nitrogen species can lead to widespread cell damage (Gutteridge and Halliwell 1989; Pratico et al. 2001; Pratico and Sung 2004). Classical activation also causes the release of proteolytic enzymes that can lead to deterioration of the extracellular matrix (such as metalloproteinases, collagenases, and furin), thus degrading cellular integrity and leading to easier destruction of the cell (Chandler et al., 1995; Maeda and Sobel, 1996; Rosenberg et al., 2001; Rosenberg, 2009; Shiryaev et al., 2009). It makes sense then that prolonged up-regulation of pro-inflammatory cytokines, like LPS, is accompanied by a decrease in synaptic plasticity, as demonstrated by inhibition of long-term potentiation (LTP) both *in vitro* and *in vivo* (Lynch, 2010), as well as a deficit in spatial learning (Oitzl et al., 1993; Hein et al., 2010). To ensure there is negative feedback control, macrophages can assume an alternative activation phenotype for inflammation resolution (Colton, 2009).

5.2. Alternative (M2) Activation

Alternative Activation is induced by Th2 cell-derived cytokine activation of M2 macrophages. This activation leads to the enhanced expression of genes meant for inflammation resolution, immunomodulation, homeostasis, scavenging, angiogenesis, and wound healing. These include genes that repair damage to the extracellular matrix, such as arginase 1 (ARG1) (Jimenez et al., 2008; Gomi et al.), mannose receptor (Akiyama et al., 2000), found in inflammatory zone 1 (FIZZ1), and chitinase 3-like 3 (YM1) (Raes et al., 2002; Colton et al., 2006a). They release high levels of anti-inflammatory cytokines like IL-10, IL-4, IL-13, and TGF-β, and low levels of pro-inflammatory cytokines. M2

macrophages are further characterized into sub-classifications, M2a, M2b, and M2c. M2a macrophages are designed for inflammation resolution and phagocytosis and are induced by IL-4, IL-13, YM1, and ARG1. IL-4 is a particularly important cytokine for M2a skewing (Maher et al., 2005; Nolan et al., 2005; Lyons et al., 2007a). Microglia stimulated by IL-4 have a decrease in TNF-α production and an increase in secretion of insulin-like growth factor-1 (IGF-1), and they also induce neurogenesis *in vitro* (Butovsky et al., 2005; Butovsky et al., 2006b). M2b macrophages clear away reactive oxygen and nitrogen species released during M1 activation, express Il-10 and CCL1 and they are skewed by immune complexes and TLR or IL-1R agonists (Mantovani et al., 2004). M2c macrophages are for the repair and tissue remodeling (wound healing), express CCL16, CCL17, CCL18, CXCL13, CCR2, and CCR5, and are skewed by IL-10 and glucocorticoid hormones (Mantovani et al., 2004).

6. Classification of Microglial Activation

Microglia are members of the monocytic-macrophage family. Like macrophages, microglia adopt similar activation phenotypes in response to CNS insult. Table 1 characterizes microglial activation states M1, M2a, and M2c by denoting their specific ligands and markers and outlining their effects on neurogenesis, synaptic plasticity, and spatial learning based on *in vitro* and *in vivo* experiments, which will be discussed below. Our lab recently identified that resting microglia adopted the M2c phenotype (unpublished observation), showing high expression of TGF-β1, extracellular matrix-related genes, and expression of IL-10. Microglial activation phenotypes switch from M2 to M1 during disease progression. Increased expression of pro-inflammatory cytokines and chemokines is likewise accompanied by M1-skewed microglial activation in the human AD brain (Hoozemans et al., 2006). These findings were reproduced in some AD mouse models, such as the APP +PS1 mouse (Jankowsky et al., 2004), which demonstrated that there was a distinctive shift from M2 to M1 microglial activation in the hippocampus of aged rodents (Jimenez et al., 2008). It was found in aged rats, for example, that IFN-γ increased with age, while Il-4 decreased (Nolan et al., 2005; Maher et al., 2006), suggesting an increased classical activation phenotype over alternative with age. This microglial phenotype switch from M2c to M1 was also demonstrated by *in vivo* intracerebroventricular injection of LPS into mouse brains as determined by changes in the gene expression of M1 markers (CCL5, CCL11, CXCL9, CXCL10, CXCL11, CXCL16, CD16, IL-12, AND IL-23) and M2c markers (Scavenger Receptor A, Scavenger Receptor B, CD14, CCR2, fibrinogen, collagen, and SOCS3) (Kopydlowski et al., 1999; Mantovani et al., 2004; Lund et al., 2006; Qin et al., 2006; Baker et al., 2009; Villeda et al., 2011).

Further evidence from APP mice and human monocyte-derived macrophages and microglia showed that, while an increase in M1 activators, like IFN-γ receptor and TNF-R1, led to neuroinflammation and inhibited clearance of Aβ, an increase in M2a or M2c activators enhanced Aβ clearance (He et al., 2007; Yamamoto et al., 2007; Yamamoto et al., 2008). The same switch was seen in LPS-stimulated primary microglia (Lund et al., 2006). IL-10 is a modulator of M2c microglial activation (Mantovani et al., 2004). It was found that IL-10 mediated anti-inflammatory responses including decreasing glial activation and production of proinflammatory cytokines (Plunkett et al., 2001). With gene delivery of IL-10 into APP

+PS1 mice, there was suppression of astro/microgliosis and a restoration of impaired spatial learning and neurogenesis, and while there was no reduction of β-amyloidosis, there was enhanced vascular transport of Aβ (Kiyota et al., 2011). IL-4, on the other hand, is an important modulator of M2a microglial activation (Mantovani et al., 2004). Gene delivery of IL-4 into APP+PS1 mice partially suppressed glial accumulation in the hippocampus, directly enhanced neurogenesis, restored impaired spatial learning, and also reduced Aβ deposition (Kiyota et al., 2010). Gene delivery of either IL-4 or IL-10 also reversed the LPS-induced deficit in LTP in the rat hippocampus (Lynch et al., 2004; Nolan et al., 2005). These findings and more are outlined in Table 2, which briefly summarizes the results of cytokine modulation on neuroinflammatory effects in AD mouse models. As can be seen in Table 2, APP mice encompass both M1 and M2c phenotypes, suggesting that the expression of the APP gene induces the up-regulation of both pro- and anti-inflammatory cytokines. Also note the contradictory findings in $NOS2^{-/-}$ mice. It was previously found that APP mice crossed with a $NOS2^{-/-}$ exhibited an M1 microglial activation phenotype and enhanced β-amyloidosis and impaired spatial/ contextual learning (Benzing et al., 1999; Apelt and Schliebs, 2001; Abbas et al., 2002). In the most recent publication, however, Kummer et al found that APP+PS1 mice crossed with $NOS2^{-/-}$ had decreased β-amyloidosis and improved spatial/ contextual learning compared to APP+PS1 mice (Kummer et al., 2011). This may be due to their use of the APP+PS1 model instead of the APP-only mouse and differences in nitration of Aβ42. These findings demonstrate that there is an important role for M2a and M2c activators in microglial activation and clearance of Aβ *in vivo*. Although it is well established that there is a large immune response component to AD, it is still not completely understood which activation phenotype affects the onset or progression of the disease and which should be the therapeutic target. The failure of anti-inflammatory drugs, like non-steroidal anti-inflammatory drugs (NSAIDs), to halt the progression of AD drives the need for more research into the link between neuroinflammation and AD (Firuzi and Pratico, 2006; Martin et al., 2008; Cole and Frautschy, 2010). This could be due to the suppression of, not only pro-inflammatory, but also anti-inflammatory activation by endogenous molecules, inactivating the beneficial effect of M2a or M2c-skewed microglial functions. Microglial activation is a prominent feature of AD and serves as the driving force behind inflammation, and has recently been suggested to play a role in both neuroprotection and neurogenesis (Butovsky et al., 2006b; Zhao et al., 2006; Figueiredo et al., 2008; Shein et al., 2008; Xapelli et al., 2008; Gomi et al., 2011), making researchers question the exact nature of its association with AD pathology.

7. Neurogenesis

Adult neurogenesis is the process of neuronal proliferation and maturation in specific brain regions, and it is not only involved in CNS maintenance but also in the formation of new memories that new evidence suggests may be linked to synaptic plasticity affected by environmental or behavioral factors (Bruel-Jungerman et al., 2007; Deng et al., 2009; Deng et al., 2010; Tronel et al., 2010). Neural stem cells (NSCs) are always present in the adult CNS by self-renewal where they have the ability to differentiate into neurons, astrocytes, and oligodendrocytes. However, the process is strictly controlled by local signaling that keeps the production of new neurons to a very low level (Dayer et al., 2005; Tamura et al.,

2007). The production of new neurons in adulthood is mainly seen in the subventricular zone (SVZ), where neuroblasts migrate to the olfactory bulb, and the subgranular zone (SGZ) of the hippocampal dentate gyrus, where the neurons are involved in hippocampal cell maintenance, the process of short-term memory formation and learning, and the regulation of mood (Ming and Song, 2005; Franklin and Ffrench-Constant, 2008). These areas have a network with high demand for the production of new neurons because they are constantly exposed to novel stimuli (Carpentier and Palmer, 2009). Only a small subset of NPCs created in the SGZ reach maturity after integration into the neural network, meaning a majority of the newborn cells undergo apoptosis within the first four days after creation (Sierra et al., 2010). It was shown by a number of researchers that exposure to novel smells in the olfactory bulb stimulated the production and retention of new neurons (Magavi et al., 2005; So et al., 2008), and it was likewise shown in the hippocampus that environmental enrichment, physical activity, and the act of learning promoted the production of new neurons (Emsley et al., 2005; Duan et al., 2008). Oddly enough, both depression and olfactory deficits are early indications of degeneration in both AD and Parkinson's disease (PD) (Bruck et al., 2004; Hawkes, 2006; Gabryelewicz et al., 2007; Matsuda, 2007; Poewe, 2008). In fact, in co-cultures of resting or IL-4-activated microglia, NPCs expressing mutant PS1 variants have inhibited neuronal proliferation and differentiation compared to NPCs expressing wild-type human PS1, suggesting that there is a specific link between components causing AD and neurogenesis (Choi et al., 2008).

8. The Effect of Neuroinflammation on Neurogenesis

8.1 M1 microglial activation and neurogenesis

Neurogenesis can be challenged by a number of factors that induce the immune system response including chronic stress, depression, injury, and neuroinflammation. The chronic infusion or even single injection of M1 pro-inflammatory response-inducing ligand, such as LPS, has been shown to cause M1 microglial activation and acute neuroinflammation that caused the subsequent inhibition of neurogenesis in the hippocampi of adult rodents (Ekdahl et al., 2003; Monje et al., 2003; Walter et al., 2011). This M1-induced disruption of neurogenesis is very specific. Proliferation of NPCs is unaffected by neuroinflammation. As previously stated, a majority of newborn cells in the SGZ will undergo apoptosis within the first four days of life, and those apoptotic cells will be cleared by microglia through phagocytosis, a process unperturbed by inflammation (Sierra et al., 2010). For example, LPS-induced suppression of neurogenesis did not affect the production and proliferation of NSCs; it negatively affected NSC capability for maturation and survival (Ekdahl et al., 2003; Bastos et al., 2008), again suggesting that the pro-inflammatory cascade affects the maturation and survival of new neurons rather than their proliferation (Ekdahl et al., 2003; Monje et al., 2003; Bastos et al., 2008). IFN-γ gene expression in *in vitro* NSC cultures showed the same reduction in differentiation (Ekdahl et al., 2003; Monje et al., 2003; Walter et al., 2011). This disruption in survival may be due to the abnormal synaptic morphology of neurons differentiated during the inflammatory state (Jakubs et al., 2008). Another possibility is the mitochondrial damage caused by neuroinflammation. Neural progenitor cells (NPCs) require energy in the form of ATP produced by mitochondria to be able to differentiate into neurons (Bernstein and Bamburg, 2003). Pro-inflammatory molecules like

TNF-α and IL-6 have been shown to contribute to mitochondrial dysfunction during brain inflammation both *in vitro* and *in vivo* (Stadler et al., 1992; Zell et al., 1997; Behrens et al., 2008; Samavati et al., 2008). This lack of proper mitochondrial production of ATP due to damage-induced up-regulation of pro-inflammatory factors may contribute to the decrease in neural differentiation in AD. The accumulation of toxic Aβ42 may also contribute to the reduction of NSC renewal in later inflammatory stages. In *in vitro* cultures of NPCs, it was found that aggregated Aβ42 inhibited neuronal differentiation (Haughey et al., 2002). Together, these studies suggest that, while AD pathology may at first enhance synthesis of new neurons as a compensatory mechanism to replace lost neurons, it may in turn reduce neuronal maturation.

8.2 M2 Microglial Activation and Neurogenesis

The suppression of M1 activation by NSAIDs, glatiramer acetate, or IL-4 gene delivery in the APP, PS1, or APP+PS1 mouse brain restored the suppression of neurogenesis seen in the SGZ (Wen et al., 2004; Chevallier et al., 2005; Butovsky et al., 2006a; Butovsky et al., 2006b; Kiyota et al., 2010). The M2 cytokines mediate the neuroprotective responses of microglia: IL-4 stimulation of microglia reduced the production of TNF-α and up-regulated production of IGF1, an important pro-neurogenic factor that induce subsequent neurogenesis (Butovsky et al., 2005; Butovsky et al., 2006b). In accord, we recently identified that IL-10-stimulated microglia enhanced proliferation but not differentiation of NSCs *in vitro* (Kiyota et al., 2011). As previously stated, IL-10 is an M2c ligand. Stimulation of microglia by an M2a ligand, IL-4, on the other hand, enhanced neural differentiation (Kiyota et al., 2010). Thus, combined treatment of these anti-inflammatory molecules with growth factors like IGF-1 or fibroblast growth factor-2 (FGF-2) may be able to restore neurogenesis, in terms of both proliferation and differentiation, and restore neurocognitive functionality in AD patients.

8.3 Neurogenesis in Aging and AD

One study recently demonstrated that an age-dependent increase in specific blood-borne factors associated with M1 microglia, as shown by the presence of the M1 marker, CCL11, may contribute to the inhibition of neurogenesis in healthy aging humans, as was seen when young mice were joined to the systemic environments of old mice by heterochronic parabiosis. This also resulted in decreased synaptic plasticity and impaired contextual fear conditioning, spatial memory, and learning (Villeda et al., 2011). There have been several contradictory reports that show how neurogenesis is particularly altered in the AD brain as well (for review, see (Waldau and Shetty, 2008)). Investigators have demonstrated that, while there is some reduction in neuronal maturation in the pre-senile post-mortem AD hippocampus, there is an increase in cellular proliferation in the hippocampus (Jin et al., 2004; Boekhoorn et al., 2006). Therefore, despite the supposed increase in neurogenesis due to increased proliferation, there is an overall reduction in neurogenesis because these newly-proliferated cells do not mature. The chronic neuroinflammation seen in AD has been shown to be the major contributor to overall suppression of neurogenesis in the SVZ and SGZ (Monje et al., 2003; Hoehn et al., 2005; Deng et al., 2010). The data from studies of microglial and inflammatory activation yielded complementary results to those found in mouse models above.

9. Neuron-Microglia Interaction through CD200 - CD200R Signaling

9.1 CD200 and CD200R

CD200 is a type I transmembrane glycoprotein with an immunoglobulin superfamily (IgSF) domain (Clark et al., 1985). It is expressed on a number of cells involved in the immune response, including T cells, B cells, and particularly in neurons in the brain (McMaster and Williams, 1979; Barclay, 1981; Webb and Barclay, 1984), and it is over-expressed in some forms of cancer cells as a means to avoid immune attack (Kretz-Rommel et al., 2007; Moreaux et al., 2008; Siva et al., 2008). Its short cytoplasmic tail suggests that its recognition domain is largely extracellular (Clark et al., 1985). The CD200R is expressed largely on cells of myeloid lineage, namely, microglia (Barclay, 1981; Koning et al., 2010). Like CD200, it is a cell surface glycoprotein with IgSF domains and a single transmembrane region (Wright et al., 2000). Unlike CD200, however, it has a large cytoplasmic region allowing for intracellular signaling initiated by tyrosine phosphorylation (Wright et al. 2000).

In order for CD200 to activate anti-inflammatory signals via CD200R, there must be an interaction between the extracellular domains of CD200 and CD200R (Hatherley and Barclay, 2004; Chen and Gorczynski, 2005). While the CD200R does not contain an immunotyrosine-based inhibitory motif (ITIM) in its cytoplasmic domain, it behaves as an inhibitory receptor on myeloid cells (Ravetch and Lanier, 2000). ITIMs are induced by ligands and lead to subsequent tyrosine phosphorylation, usually by Src family kinases, which allows for the recruitment of phosphatases with a Src homology 2 (SH2) domain (Ravetch and Lanier, 2000). CD200 interacts with CD200R through an immunoregulatory signal on its N-terminal Ig domain where tyrosine phosphorylation of the cytoplasmic NPxY motif on CD200R leads to a sequence of signaling events and interaction with PTB-binding domains with recruited adaptor proteins downstream of tyrosine kinase 1 and 2 (Dok1 and Dok2) (Wright et al., 2000; Hatherley and Barclay, 2004). After binding to Dok1 and Dok2, the SH2-containing inhibitory signaling molecule inositol 5-phosphatase (SHIP) and RAS p21 protein activator 1 (RasGAP) are recruited (Zhang et al., 2004). The CD200-CD200R interaction negatively modulates myeloid cells, supposedly through binding of Dok2 to phosphorylated NPxY and recruitment of RasGAP and subsequent inhibition of Erk, p38 MAPK, and JNK pathways (Mihrshahi et al., 2009). This is the signaling pathway by which CD200 activates its anti-inflammatory actions.

9.2 The Role of CD200 in Microglial Activation and AD

As stated above, CD200 is mainly expressed in neurons in the brain (Webb and Barclay, 1984), and the CD200R is expressed on astrocytes and cells of the myeloid lineage, including dendrites, macrophages, neurophils, and microglia (Hoek et al., 2000; Wright et al., 2000; Broderick et al., 2002; Wright et al., 2003). Both have wide distribution and expression throughout the brain. CD200 expression decreases with age where it is simultaneously associated with increased microglial activation (Lyons et al., 2007b). It is likewise decreased in the brains of AD patients and in the brains of Aβ-treated mice (Lyons et al., 2009; Walker et al., 2009). Interestingly, hippocampal slices from mice lacking CD200 also showed significant impairments in synaptic plasticity, specifically in LTP, tying

the age-dependent decrease in CD200 with the decreased ability to form new memories in AD patients (Costello et al., 2011).

Several pieces of evidence point to the importance of CD200 in both the immune response and inflammation in AD. It has been demonstrated by many from both *in vitro* and *in vivo* models that CD200 is an important regulator of microglial activation and inflammation. Much of this research is generated from work on mouse models of inflammatory diseases, like the experimental autoimmune encephalomyelitis (EAE) model for MS or experimental autoimmune uveoretinitis (EAU) mice. Several studies have demonstrated in these mouse models that CD200 regulates CNS autoimmune disorders by showing that blockage of CD200 or CD200R causes increased inflammation and tissue damage while treatment with agonistic anti-CD200R antibodies ameliorated such symptoms (Banerjee and Dick, 2004; Chitnis et al., 2007; Copland et al., 2007). Other *in vivo* and *in vitro* data come from mice lacking the CD200 or CD200R gene ($CD200^{-/-}$ and $CD200R^{-/-}$). *In vitro* data from blocked CD200R on macrophages expressing CD200 from EAU mice, for example, showed an enhancement of IFN-γ-induced release of IL-6 and neuronal cell death (Copland et al., 2007). Mice that were deficient in CD200 showed enhanced spontaneous inflammation and exaggerated inflammatory responses to injurious stimuli, like what one would observe in EAE (Hoek et al., 2000). Complimentary evidence showed that mice lacking CD200R expression had enhanced production of TNF-α and inflammatory responses to LPS, despite their continued expression of CD200 (Boudakov et al., 2007).

In addition to those findings from models of inflammation, other data show that there is a clear correlation between CD200 levels and other markers of pro- or anti-inflammation, namely IL-4. IL-4, the important anti-inflammatory signaling molecule for M2a activation of microglia, regulates the expression of downstream CD200. In both *in vitro* and *in vivo* studies from mouse and human tissue, it has been shown that a lack of IL-4 is correlated with a decrease in CD200 expression, and an increase in IL-4 results in an increase in CD200 expression (Lyons et al., 2007b; Lyons et al., 2009; Koning et al., 2010). In animal models of AD, where the age-related increase in microglial activation was accompanied by an age-related or Aβ-induced decrease in CD200 expression, IL-4 treatment was able to restore that deficit (Lyons et al., 2007b; Lyons et al., 2007a; Kiyota et al., 2010). These tissues and glia from AD models lack IL-4 and have enhanced inflammatory responses to LPS (Lyons et al., 2009). As mentioned earlier, IL-4 gene therapy to APP+PS1 mice enhanced clearance of Aβ and improved spatial learning, but only in the pre-symptomatic stages of the disease (Kiyota et al., 2010). This suggests that IL-4 signaling may already be compromised at the later disease stages due to the decreased expression of CD200 in the aged and the AD brain. This is the reason why CD200 is a more plausible therapeutic target than IL-4, and may have a therapeutic effect on post-symptomatic AD mouse models.

Worth mentioning are findings from other disease models that allude to the importance of CD200. A number of different cancer cells over-express CD200, theoretically as a means to alleviate T-cell-mediated cytotoxicity (Kretz-Rommel et al., 2007; Moreaux et al., 2008; Siva et al., 2008). Melanoma cells had increased CD200 expression, and this was correlated with their potential to be metastatic. It was shown that cancer patients' myeloma CD200 expression in turn correlated with their likelihood for survival (Moreaux et al., 2006;

Petermann et al., 2007; Siva et al., 2008). This makes CD200 an excellent target in cancer therapy as well. It may be possible to target cancer cells over-expressing CD200 with an anti-CD200 antibody. These and all of the above findings show that there are good reasons for further research to investigate the role of CD200 in the brain. While there are some clear correlations seen in aging and in disease models, such as MS, AD, and cancer, the connection between CD200 and these diseases is still unclear. CD200 has never been tested for its therapeutic potential in AD animal models. The other issue brought to light by the results of the afore-mentioned IL-4 study is the relationship between neuroinflammation and neurogenesis in AD. Our lab and other researchers are currently looking into potential CD200 drug treatments or animal models to figure out the connection between IL-4 signaling, CD200, and neurogenesis in AD.

9.3 The Role of Dok in CD200R Signaling

One possible mechanism to look into is the Dok signaling pathway of the CD200R. As previously stated, when CD200 binds to CD200R, the interaction negatively modulates myeloid cells through binding of Dok2. While there has not been very much research on Dok proteins, they are involved in immune suppression signaling. They are expressed on peripheral T cells and most thymocytes, and act as negative regulators of T cell response signaling (Yasuda et al., 2007). Mice that lack Dok1 and/or Dok2 showed increased production of pro-inflammatory molecules, like TNF-α and NO, and enhanced responses to inflammation-inducing signals like those from IFN-γ and LPS (Shinohara et al., 2005; Yasuda et al., 2007).

These findings are similar to those seen in $CD200^{-/-}$ mice whose lack of ligand or receptor expression correlated with increased neuroinflammation and tissue damage and production of TNF-α in response to LPS. There is no published study to date that shows the regulating relationship between CD200R and Dok proteins in microglia and inflammation. CD200R is believed to act via Dok2 signaling, but it is still unknown which is the controlling mechanism. Figure 1 outlines the unresolved pathways that CD200/CD200R/Dok2 signaling may follow to attain its anti-inflammatory effects. While $Dok1/2^{-/-}$ mice seem to have similar phenotypes to CD200 or $CD200R^{-/-}$ mice, it has not yet been tested whether treatment of $Dok1/2^{-/-}$ mice with CD200 can compensate for maintenance of immune system homeostasis (Fig. 1).

One important issue worthy of mentioning, however, is the limitations of using mouse models for modeling human diseases. Koning et al did a comparative study of CD200R expression in the mouse and the human, and found that, while induction of CD200R expression in human macrophages was dependent on IL-4, mouse CD200R expression was not (Koning et al., 2010). Induction of mouse CD200R expression was not discovered, but it was theorized that it involved site-specific combinations of cytokines (Snelgrove et al., 2008). Therefore, while the CD200R may be a suitable indicator of alternative activation in humans, this may be a species-specific mechanism. This shows that research into the controlling mechanism between CD200R and Dok signaling may be a key finding.

10. Concluding Remarks

Research has still been unable to pinpoint a single cause for the neuronal death and synaptic dysfunction that leads to the cognitive decline seen in AD. Increasing evidence suggests that the cause is an interaction between the down-regulation of important immune regulatory components, increased inflammation, and decreased neurogenesis, and it is becoming more widely believed that inflammation is the major culprit in this interaction. This neuroinflammation is orchestrated by M1-skewed microglial activation often associated with loss of neurons in specific brain regions due to the production of damaging reactive oxygen species and toxic intermediates (Gutteridge and Halliwell 1989; Pratico et al. 2001; Pratico and Sung 2004). Alternative M2 microglial activation, on the other hand, is important for resolution of this inflammation. M2 activation causes the release of anti-inflammatory cytokines like IL-4, which is important for M2a microglial activation, and IL-10, which is important for M2c.

There is a characteristic switch from M2 to M1 microglial activation in the brain that occurs both with age and with disease progression. There is an up-regulation of pro-inflammatory cytokines and a reduction in anti-inflammatory cytokines and proteins, like CD200 (Lyons et al., 2007b; Lyons et al., 2009; Walker et al., 2009). CD200 interacts with CD200R via the Dok signaling pathway to activate anti-inflammatory signals, and its age-dependent decline is associated with increased microglial activation (Lyons et al., 2007b). A lack of CD200 or Dok results in increased neuroinflammation in the brain (Shinohara et al., 2005; Yasuda et al., 2007). This is seen in both rodent and human brain tissue. Treatments with specific M2a or M2c anti-inflammatory cytokines, like IL-4 or IL-10, can improve deficits seen as a result of up-regulated inflammatory responses, and restore CD200 expression which is specific to IL-4 (Lyons et al., 2007b; Lyons et al., 2007a; Kiyota et al., 2010). Neuroinflammatory states have also been shown to greatly decrease neurogenesis in the SVZ and SGZ, which may explain the deficit in short-term memory formation in AD patients. Evidence suggests that M1 microglial activation suppresses, not the proliferation of NSCs, but the differentiation of NPCs (Waldau and Shetty, 2008). Treatment with M2 cytokines or proteins like CD200, IL-4, or IL-10, and growth factors like FGF-2 can possibly restore that deficit.

There is still no successful therapy available to halt and reverse the devastating neurodegeneration seen in AD, but the evidence leads one to conclude that the best treatment for AD may be a combined therapeutic with anti-inflammatory and pro-neurogenic components. While none have been thoroughly tested, IL-4, IL-10, CD200, FGF-2, and Dok signaling proteins have proven to be promising targets for further research. Regardless of the various potentials of these therapeutic targets, it is clear that there is still a lack of understanding of the complicated relationship between inflammation and AD that warrants further investigation.

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Abbreviations

Aβ	amyloid β-peptide
AD	Alzheimer's disease
ADAM	a disintegrin and metalloproteinase
AICD	APP intracellular domain
APP	amyloid precursor protein
ARG1	arginase 1
BACE	β-site APP converting enzyme
BrdU	bromodeoxyuridine
CD200	cluster of differentiation 200 (aka OX2)
CNS	central nervous system
DAMP	damage-associated molecular pattern
Dok	downstream of tyrosine kinase
Erk	extracellular signal-regulated kinase
EAE	experimental autoimmune encephalomyelitis
EAU	experimental autoimmune uveoretinitis
FasL	Fas ligand
FGF-2	fibroblast growth factor-2
FIZZ1	found in inflammatory zone 1
HPA	hypothalamo-pituitary-adrenal
IGF-1	insulin-like growth factor-1
IgSF	immunoglobulin superfamily
IFN-γ	interferon-γ
IL	interleukin
ITIM	immunotyrosine-based inhibitory motif
JNK	c-Jun N-terminal kinase
LPS	lipopolysaccharide
LTP	long-term potentiation
MAPK	mitogen-activated protein kinase
MDP	muramyl dipeptide
MR	mannose receptor
MS	multiple sclerosis

NFT	neurofibrillary tangle
NLR	NOD-like receptor
NO	nitric oxide
NOD	nucleotide oligomerization domain
NOS	nitric oxide synthase
NPC	neural progenitor cell
NSAID	non-steroidal anti-inflammatory drug
NSC	neural stem cell
PAMP	pathogen-associated molecular pattern
PD	Parkinson's disease
PEN-2	presenilin enhancer-2
PRR	pathogen recognition receptor
PS	presenilin
RasGAP RAS	p21 protein activator 1
RIG1	retinoic acid-inducible gene-1
RLR	RIG1-like receptor
SGZ	subgranular zone
SH2	Src homology 2
SHIP	SH2-containing inhibitory signaling molecule inositol 5-phosphatase
SVZ	subventricular zone
TGF-β	transforming growth factor-β
TLR	toll-like receptor
TNF-α	tumor necrosis factor-α
YM1	chitinase 3-like 3
WT	wild type

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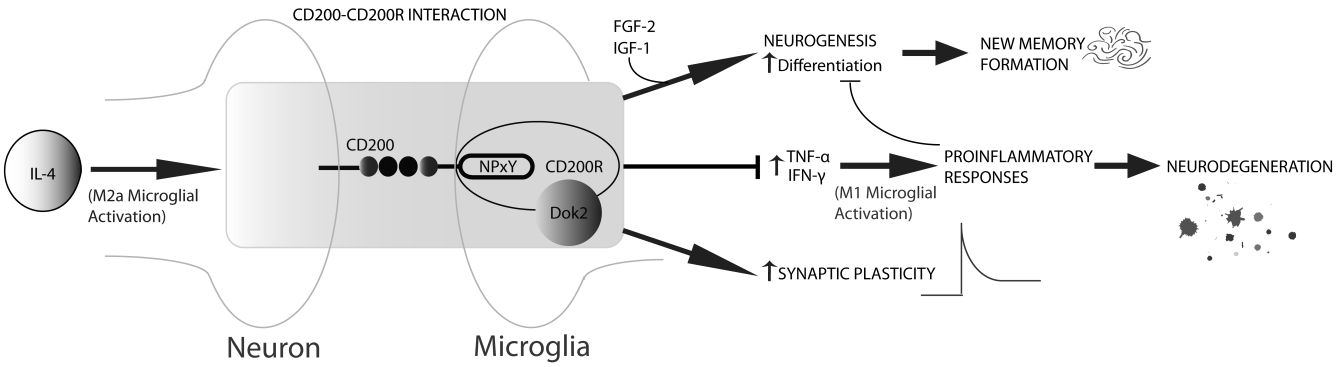

Fig. 1. Effects of CD200/CD200R/Dok2 Signaling

M2a-skewing anti-inflammatory cytokine IL-4, which initiates the inter-cellular interaction between CD200 on neurons and CD200R on microglia. CD200R signaling acts via Dok2 to contribute to the regulation of three distinct, but unsolved pathways that result in the following: 1) enhanced neurogenesis by up-regulation of differentiation of NPCs to assist in new memory formation; 2) inhibited release of pro-inflammatory molecules that initiate M1 microglial activation and subsequent neurodegeneration; and 3) enhanced synaptic plasticity, particularly LTP.

Table 1

Characterization of microglial activation states based on *in vitro* and *in vivo* experiments

	Microglial Activation State		
Classification	**M1**	**M2a**	**M2c**
Phenotype	Classical/pro-inflammatory Activation	Alternative Activation, anti-inflammatory	Deactivation/Wound-Healing
Ligands	IFN-γ[3], TNF-α[3], TLR ligand[30, 36]; Aβ[22, 28, 35]	IL-4[12, 25, 26, 27, 31], IL-13[29]	IL-10[12], glucocorticoid hormones[27], TGF-β[12]
Markers	NOX[4], NOS2[14], TNF[3], IL-6[3], IL-12[3], IL-1β[3], CCL2[3], CCL5[21], CCL11[37], STAT3[5, 16]	ARG1[13, 18], MR[9, 34], FIZZ1[9, 34], YM1[9, 34], IGF-1[6, 7]	SOCS3[1, 33], MR[9, 34], IL-10[12], TGF-β[12]
Neurogenic Effect	Inhibition of NSC differentiation and maturation [2, 10, 11, 17, 29, 38]	Enhanced NSC differentiation[6, 7, 19]	Enhanced NSC proliferation[20]
Neuroprotection	Enhanced neurotoxicity, ECM damage [14]	Anti-inflammatory neuroprotection, phagocytosis[8]	Deactivation of glial inflammation[27]
Synaptic Plasticity	CA1 LTP↓ [23]	CA1 LTP↑ [31]	CA1 LTP↑ [24]
Spatial Learning	MWM↓[15, 32]	RAWM↑ [19]	RAWM↑ [20]
References	[1]Baker et al 2009; [2]Bastos et al. 2008; [3]Benoit et al. 2008; [4]Brown 2007; [5]Burton et al. 2011; [6]Butovsky et al. 2005; [7]Butovsky et al. 2006b; [8]Carpentier and Palmer 2009; [9]Colton et al. 2006; [10]Deng et al. 2010; [11]Ekdahl et al. 2003; [12]Elenkov and Chrousos 2002; [13]Gomi et al. 2011; [14]Gutteridge and Halliwell 1989; [15]Hein et al. 2009; [16]Heinrich et al. 1998; [17]Hoehn et al. 2005; [18]Jimenez et al. 2008; [19]Kiyota et al. 2010; [20]Kiyota et al. 2011; [21]Kopydlowski et al 1999; [22]Lotz et al. 2005; [23]Lynch 2010; [24]Lynch et al. 2004; [25]Lyons et al. 2007a; [26]Maher et al. 2005; [27]Mantovani et al. 2004; [28]E.G. McGeer and McGeer 2010; [29]Monje et al. 2003; [30]Nagai et al. 2002; [31]Nolan et al. 2005; [32]Oitzl et al. 1993; [33]Qin et al 2006; [34]Raes et al. 2002; [35]Reed-Geaghan et al. 2009; [36]Takeda and Akira 2004; [37]Villeda et al. 2011; [38]Walter et al. 2011		

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Table 2

Microglia Activation in AD Mouse Models

Modified Phenotype	Model	Cytokine Modified	Inflammation	Neurogenesis	Spatial/ Contextual Learning	β-amyloidosis	References
	APP		↑ IFN-γ, IL-1β, IL-6, TGF-β, IL-10, IL-12, ↓ IL-4	↑↓	↓	+	(Abbas et al. 2002; Apelt and Schliebs 2001; Benzing et al. 1999)
	APP+PS1		↑ TNF-α, IL-6, IL-12, IL-1β, IL-1α	↓	↓	++	(Patel et al. 2005)
	3×Tg-AD		↑ TNF-α	↓	↓	+	(Janelsins et al. 2005)
M1↓	APP	DN C3 TG	↓ Microgliosis	ND	ND	↑	(Wyss-Coray et al. 2002)
M1↑	APP	CCL2 TG	↑ Astro/microgliosis	ND	↓	↑	(Kiyota et al. 2009a; Song et al. 2011)
M1↓	APP+PS1	DN CCL2 GT	↓ Astro/microgliosis	ND	↑	↓	(Kiyota et al. 2009b)
M1 → M2b	APP+PS1	× $CD14^{-/-}$	↓ Microgliosis, FIZZ1, YM1, ↑ TNF-α, IFN-γ, IL-10	ND	ND	↓	(Reed-Geaghan et al. 2010)
M1↓	APP	× $IFN\text{-}\gamma R^{-/-}$	↓ TNF-α, astro/microgliosis	ND	ND	↓	(Yamamoto et al. 2007)
M1↑	APP	IL-1β TG	↑ MHCII, astrogliosis	ND	ND	↓	(Shaftel et al. 2007)
M1↑	APP	× $NOS2^{-/-}$	↑ TNF-α, IL-6	ND	↓	↑	(Colton et al. 2006; Colton et al. 2008; Wilcock et al. 2008)
M1↓	APP+PS1	× $NOS2^{-/-}$	↓ Astro/microgliosis	ND	↑	↓	(Kummer et al. 2011)
M1↓	APP	× TLR-4 DN TG	↑↓ Microgliosis ↓IL-1β, IL-6	ND	↓	↑	(Jin et al. 2008; Tahara et al. 2006)
M1↓	APP	× $TNFR1^{-/-}$	↓ Astro/microgliosis	ND	↑	↓	(He et al. 2007)
M1↑	3×Tg-AD	TNF-α GT	↑ Microgliosis	ND	ND	↓	(Janelsins et al. 2008)
M2a↑	APP+PS1	IL-4 GT	↑ IL-4 ↓ Astro/microgliosis	↑	↑	↓	(Kiyota et al. 2010)
M2c↑	APP+PS1	IL-10 GT	↓ Astro/microgliosis	↑	↑	↓	(Kiyota et al. 2011)
M2c↑	APP	IL-10 GT	↓ Microgliosis	ND	↑	↓	(Hara et al. 2011)
M2c↑	APP	× TGF-β1 TG	↑ Microgliosis	ND	ND	↓	(Wyss-Coray et al. 2001)
M2c↓	APP	DN TGF-βR TG	↑ Microgliosis	ND	ND	↑	(Tesseur et al. 2006)

Modified Phenotype	Model	Cytokine Modified	Inflammation	Neurogenesis	Spatial/ Contextual Learning	β-amyloidosis	References
M2c↓	APP	DN TGF-βR TG	↑ Dendritic cells ↓ Astrogliosis	ND	↑	↓	(Town et al. 2008))

DN = Dominant negative, GT= Gene transfer, ND = Not determined, TG = Transgenic, × = cross-bred