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REVIEW

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. There is no therapy 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 in 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 such as interleukin-4 and CD200 have proven to be important anti-inflammatory mediators in the regulation of neuroinflammation in the brain, which will be discussed in detail for their therapeutic potential.

Keywords Alzheimer's disease · Microglia · Neurogenesis · Neuroinflammation

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Abbreviations

Aβ	Amyloid β-peptide
AD	Alzheimer's disease
AICD	APP intracellular domain
APP	Amyloid precursor protein
ARG1	Arginase 1
ATP	Adenosine triphosphate
CD200	Cluster of differentiation 200 (aka OX2)
CNS	Central nervous system
Dok	Downstream of tyrosine kinase
Erk	Extracellular signal-regulated kinase
EAE	Experimental autoimmune encephalomyelitis
EAU	Experimental autoimmune uveoretinitis
FGF-2	Fibroblast growth factor-2
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
MS	Multiple sclerosis
NFT	Neurofibrillary tangle
NLR	NOD-like receptor
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
PRR	Pathogen recognition receptor
PS	Presenilin
RasGAP	RAS p21 protein activator 1
SGZ	Subgranular zone
SH2	Src homology 2
SVZ	Subventricular zone
TGF-β	Transforming growth factor-β
TLR	Toll-like receptor
TNF-α	Tumor necrosis factor-α
YM1	Chitinase 3-like 3

Introduction

Alzheimer's disease (AD) is the most prevalent neurodegenerative disease, and it is characterized by progressive decline of neuro-cognitive function in mostly elderly populations (Minati et al. 2009). While the exact pathophysiology of AD has yet to be determined, it is known that aging is the greatest risk factor for development of the disease. AD presents with a 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 (Alzheimer et al. 1995; Dickson et al. 1988). AD patients also exhibit an extensive loss of synapses and neurons, namely in the temporal and frontal cortices and hippocampi (Davies et al. 1987; Scheff et al. 2006, 2007). Increasing evidence suggests that it is the aggregation of Aβ species that causes neurotoxic effects which lead to the neural, synaptic, and cognitive dysfunction seen in AD, making Aβ the target of most AD research today (Hardy and Selkoe 2002).

Amyloid Precursor Protein and Aβ Biology

Aβ is formed by the proteolytic cleavage of amyloid precursor protein (APP) (Zhao et al. 2006), 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 a disintegrin and metalloproteinase family have α-secretase activity and are implicated in the 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 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 (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 gene 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 (Baek et al. 2002; Cao and Sudhof 2001, 2004; Leissring et al. 2002). 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 (Iwatsubo et al. 1995; Jarrett et al. 1993; Lemere et al. 1996).

A large number of studies have proven that Aβ has a neurotoxic effect when aggregated in specific forms (Hardy and Selkoe 2002; Lambert et al. 1998; Walsh et al. 2002).

Its formation and buildup precedes the accumulation of hyperphosphorylated tau into NFTs and leads to synaptic dysfunction and neuronal loss (Lue et al. 1999; Mattson et al. 1998; Selkoe 1991; 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 buildup of reactive intermediates and oxygen species that lead to oxidative injury (Gutowicz 2011; Kish et al. 1992). 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 neurodegeneration in AD based on several pieces of evidence (Struble et al. 2010). Firstly, therapeutics against Aβ, though successful in removing Aβ deposits in animal models and humans, do not stop the progression of AD, meaning it is not the reversible 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 (Haass and De Strooper 1999; Seubert et al. 1992; Shoji et al. 1992), and those individuals with APP or γ-secretase gene 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 (Aizenstein et al. 2008; Bennett et al. 2006). This has led research to aim for the discovery of the other underlying factor(s) that leads to the cognitive decline in AD.

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 (Bishop et al. 2010; Loerch et al. 2008; Lu et al. 2004; Prolla 2002). This can be partly corrected by caloric restriction (Lee et al. 2000), which suggests that energy expenditure-associated oxidative stress underlies the M2 to M1 conversion in the brain. The outcome of oxidative stress can be DNA damage and reduced repair (Haigis and Yankner 2010). Highly conserved insulin/insulin-like growth factor-1 (IGF-1), mammalian target of rapamycin, and sirtuin signaling pathways regulate these cellular responses, and the aging process potentially induces their dysregulation, leading to neuroinflammation.

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 including tumor necrosis factor-α (TNF-α) in the serum of AD patients (Fillit et al. 1991) and interleukin-6 (IL-6) in brain tissue (Bauer et al. 1991, 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 (Ishii and Haga 1992; Wegiel and Wisniewski 1990; Wisniewski and Wegiel 1991); and of particular interest in this article is the down-regulated expression of an anti-inflammatory 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, 1994). Indeed, some individuals with significant 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 of 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 other disease-associated changes, such as tauopathy or the cognitive decline.

Of particular interest is the role of the microglial activation switch from the alternative to classical activation phenotype during the disease progression. This change in microglial activation skewing phenotype may be the cause of significant amounts of cortical and hippocampal atrophy that makes neurogenesis a potential target for studying ways to replenish that loss (Volobouéva and Giffard 2011). 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.

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. PRRs include Toll-like receptors (TLRs), nucleotide oligomerization domain (NOD)-like receptors (NLRs), and retinoic acid-inducible gene 1-like receptors. 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 gene transcription and synthesis of pro-inflammatory cytokines and chemokines (Bailey et al. 2006). LPS-induced inflammatory response is enhanced in aged animals in vivo (Lynch 2010; Sparkman and Johnson 2008). 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 loci of infection or injury. The lymphocytes bind to the activated endothelium and diffuse into the affected tissue. Through antigen recognition and B cell-mediated antibody production, they remove infected 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-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. Macrophages mediate 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.

Classification of Macrophage Activation: M1/M2 Switch of Activation Phenotype

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 (David 1975; Mackaness 1970; Oppenheim and Rosenstreich 1976). Macrophage activation is classified into two phenotypes: classical and alternative (Gordon 2003; Mills et al. 2000). Classical activation involves the induction of M1 macrophages by Th1 cell-derived cytokines, such as IFN-γ, TNF-α, and IL-1β, to allow cells to respond to PAMPs. M1 macrophages express opsonic receptors, such as immunoglobulin Fcγ receptors (e.g., FcγRIII) (Ravetch and Kinet 1991; Unkeless et al. 1988). 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, and corresponding

toxic intermediates, and reactive oxygen and nitrogen species (Akiyama et al. 2000; Benoit et al. 2008; Brown 2007; Burton et al. 2011; Gutteridge and Halliwell 1989; Heinrich et al. 1998; Pratico et al. 2001; Pratico and Sung 2004). 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 NF-κB and three types of mitogen-activated protein kinases (MAPKs): extracellular signal-regulated kinase (Erk), c-Jun N-terminal kinase (JNK), and p38 (Nagai et al. 2002; Takeda and Akira 2004). 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). Prolonged up-regulation of pro-inflammatory cytokines by 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 (Hein et al. 2010; Oitzl et al. 1993). To ensure there is negative feedback control, macrophages shift to alternative activation phenotype for inflammation resolution (Colton 2009).

Alternative (M2) Activation

Alternative activation is induced by Th2 cell-derived cytokine activation of 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) (Gomi et al. 2011; Jimenez et al. 2008), mannose receptor (Akiyama et al. 2000), found in inflammatory zone 1, and chitinase 3-like 3 (YM1) (Colton et al. 2006a; Raes et al. 2002). They release high levels of anti-inflammatory cytokines such as 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 (Lyons et al. 2007b; Maher et al. 2005; Nolan et al. 2005). Microglia stimulated by IL-4 have a decrease in TNF-α production and an increase in secretion of IGF-1, and they also induce neurogenesis in vitro (Butovsky et al. 2005, 2006b). M2b macrophages clear away reactive oxygen and nitrogen species released during M1 activation, express IL-10 and CCL1, and are skewed by immune complexes and TLR or IL-1R agonists (Mantovani et al. 2004). M2c macrophages play a role in 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).

Classification of Microglial Activation

Microglia are members of the monocytic lineage. Similar to macrophages, microglia adopt different activation phenotypes in response to CNS insults. While the definition of the classification is not entirely identical to those for macrophages, we adapt similar characterization to microglia. Table 1 summarizes 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 studies, 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 (Maher et al. 2006; Nolan et al. 2005), suggesting a skewed 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) (Baker et al. 2009; Kopydlowski et al. 1999; Lund et al. 2006; Mantovani et al. 2004; Qin et al. 2006; Villeda et al. 2011).

Further evidence from APP mice and human monocyte-derived macrophages and microglia showed that, while an increase in M1 activators led to neuroinflammation and inhibited clearance of Aβ, an increase in M2a or M2c

Table 1 Characterization of microglial activation states based on in vitro and in vivo experiments

Classification	Microglial activation state		
	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$\downarrow$[23]	CA1 LTP$\uparrow$[31]	CA1 LTP$\uparrow$[24]
Spatial learning	MWM$\downarrow$[15,32]	RAWM$\uparrow$[19]	RAWM$\uparrow$[20]

ECM extracellular matrix, *NOX* NADPH oxidase, *MWM* Morris water maze, *RAWM* radial arm water maze, *MR* mannose receptor, *FIZZ1* found in inflammatory zone 1

[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. (2006a), [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. (2010), [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] 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)

activators enhanced Aβ clearance (He et al. 2007; Yamamoto et al. 2007, 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). IL-10 mediates anti-inflammatory responses including decreasing glial activation and production of pro-inflammatory 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 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). Table 2 summarizes the results of cytokine modulation on neuroinflammatory effects in AD mouse models. 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 APP NOS2$^{-/-}$ mice. It was previously found that APP mice in NOS2$^{-/-}$ background exhibited an M1 microglial activation phenotype and enhanced β-amyloidosis and impaired spatial/contextual learning (Abbas et al. 2002; Apelt and Schliebs 2001; Benzing et al. 1999). In the most recent publication, however, Kummer et al. (2011) found that APP + PS1 mice in NOS2$^{-/-}$ background had decreased β-amyloidosis and improved spatial/contextual learning compared to APP + PS1 mice. This could be due to their use of the APP + PS1 model instead of the APP-only transgene 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 in 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, such as 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 (Cole and Frautschy 2010; Firuzi and Pratico 2006; Martin et al. 2008). 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; Figueiredo et al.

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)
	3xTg-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. (2009b); Song et al. (2011)
M1↓	APP + PS1	DN CCL2 GT	↓ Astro/microgliosis	ND	↑	↓	Kiyota et al. (2009a)
M1 → M2b	APP + PS1	×CD14$^{-/-}$	↓ Microgliosis, FIZZ1, YM1, ↑ TNF-α, IFN-γ, IL-10	ND	ND	↓	Reed-Geaghan et al. (2010)
M1↓	APP	×IFN-γR$^{-/-}$	↓ 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. (2006b, 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↑	3xTg-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)
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

2008; Gomi et al. 2011; Shein et al. 2008; Xapelli et al. 2008; Zhao et al. 2006), stimulating researchers to understand the exact role in AD pathology.

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 potentially in the formation of new memories and synaptic plasticity, which are affected by environmental or behavioral factors (Bruel-Jungerman et al. 2007; Deng et al. 2009, 2010; Tronel et al. 2012). Neural stem cells (NSCs) are consistently present in the adult brain by self-renewal where they have the ability to differentiate into multiple cell lineages. However, the process is strictly controlled by local and intrinsic 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 (Franklin and Ffrench-Constant 2008; Ming and

Song 2005). 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 neural progenitor cells (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 4 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 (Duan et al. 2008; Emsley et al. 2005). Interestingly, both depression and olfactory deficits are early indications of degeneration in both AD and Parkinson's disease (Bruck et al. 2004; Gabryelewicz et al. 2007; Hawkes 2006; 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 whose cell proliferation or differentiation was enhanced by the co-culture, suggesting that there is a specific link between components causing AD and neurogenesis (Choi et al. 2008).

The Effect of Neuroinflammation on Neurogenesis

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 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 4 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 (Bastos et al. 2008; Ekdahl et al. 2003), again suggesting that the pro-inflammatory cascade affects the maturation and survival of new neurons rather than their proliferation (Bastos et al. 2008; Ekdahl et al. 2003; Monje et al. 2003). IFN-γ gene expression in NSC 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. NPCs require energy in the form of adenosine triphosphate (ATP) produced by mitochondria to be able to differentiate into neurons (Bernstein and Bamburg 2003). Pro-inflammatory molecules such as TNF-α and IL-6 have been shown to contribute to mitochondrial dysfunction during brain inflammation both in vitro and in vivo (Behrens et al. 2008; Samavati et al. 2008; Stadler et al. 1992; Zell et al. 1997). This lack of proper mitochondrial production of ATP due to 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.

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 (Butovsky et al. 2006a, b; Kiyota et al. 2010; Wen et al. 2004). 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 IGF-1, an important pro-neurogenic factor that induce subsequent neurogenesis (Butovsky et al. 2005, 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 such as 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.

Neurogenesis in Aging and AD

One study recently demonstrated that an age-dependent increase in specific blood-borne factors associated with M1

macrophages, 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 ligated 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 (Boekhoorn et al. 2006; Jin et al. 2004). 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 (Deng et al. 2010; Hoehn et al. 2005; Monje et al. 2003). The data from studies of microglial and inflammatory activation yielded complementary results to those found in mouse models above.

Neuron–Microglia Interaction through CD200–CD200R Signaling

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 (Barclay 1981; McMaster and Williams 1979; Webb and Barclay 1984). CD200 is highly 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, including microglia (Barclay 1981; Koning et al. 2010). Similar to 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 (Chen and Gorczynski 2005; Hatherley and Barclay 2004). 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 phosphotyrosine-binding domains of recruited adaptor proteins downstream of tyrosine kinase 1 and 2 (Dok1 and Dok2) (Hatherley and Barclay 2004; Wright et al. 2000). After binding to Dok1 and Dok2, the SH2-containing inhibitory signaling molecule inositol 5-phosphatase and RAS p21 protein activator 1 (RasGAP) are recruited (Zhang et al. 2004). The recruitment of RasGAP subsequently inhibitis Erk, p38 MAPK, and JNK pathways (Mihrshahi et al. 2009).

The Role of CD200 in Microglial Activation and AD

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, neutrophils, and microglia (Broderick et al. 2002; Hoek et al. 2000; Wright et al. 2000, 2003). Both molecules have ubiquitous distribution and expression throughout the brain. CD200 expression decreases with age where it is simultaneously associated with increased microglial activation (Lyons et al. 2007a). 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 autoimmune 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, such as 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 EAU mice lacking in CD200, 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 the facial nerve transection (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 inflammation, namely IL-4. IL-4, the prototypical anti-inflammatory signaling molecule for M2a activation, regulates the expression of 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 (Koning et al. 2010; Lyons et al. 2007a, 2009). 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 (Kiyota et al. 2010; Lyons et al. 2007a, b). 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 delivery 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. Thus 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 is negatively 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. While there are some clear correlations seen in aging and in disease models, such as MS, AD, and cancer, the pathophysiologic connection between CD200 and these diseases is still unclear.

The Role of Dok in CD200R Signaling

When CD200 binds to CD200R, the interaction negatively modulates myeloid cells through binding of Dok2. 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, such as TNF-α and nitric oxide, 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, tissue damage and production of TNF-α in response to LPS. There is no published study that shows the signaling mechanism CD200R and Dok proteins in microglia and inflammation. Figure 1 outlines the unresolved pathways that CD200/CD200R/Dok2 signaling may follow to attain its anti-inflammatory effects between neurons and microglia. 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, however, is the limitations of using mouse models for modeling human diseases. Koning et al. (2010) did a comparative study of CD200R expression in the mouse and the human macrophages, and found that, while induction of CD200R expression in human macrophages was dependent on IL-4, mouse CD200R expression was not. Induction of mouse CD200R expression was proposed 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.

Concluding Remarks

Research has still been unable to pinpoint the exact cause for the neuronal death and synaptic dysfunction that leads to the cognitive decline seen in AD. Increasing evidence suggests that the cause is potentially an interaction between the immune regulatory components and neurogenesis, and it is becoming more widely believed that inflammation is the major culprit in this interaction. 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

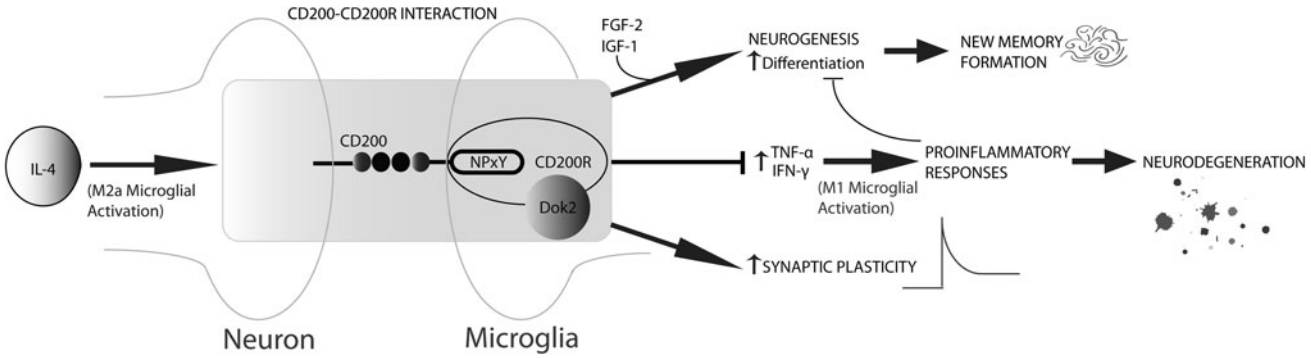

Fig. 1 Effects of CD200/CD200R/Dok2 signaling. M2a-skewing cytokine IL-4, which enhances the inter-cellular interaction between CD200 on neurons and CD200R on microglia. CD200R signaling acts via Dok2 to contribute to the regulation of three distinct, but unsolved pathways that result in the following: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

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 namely 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 disease progression. There is an enhancement of pro-inflammatory cytokines and a reduction in anti-inflammatory cytokines and proteins, such as CD200 (Lyons et al. 2007a, 2009; Walker et al. 2009). CD200 interacts with CD200R, which recruits Dok to activate anti-inflammatory signaling, and its age-dependent decline is associated with increased microglial activation (Lyons et al. 2007a). A lack of CD200 or Dok results in increased neuroinflammation in the brain (Shinohara et al. 2005; Yasuda et al. 2007). Treatments with specific M2a or M2c anti-inflammatory cytokines, such as IL-4 or IL-10, can improve neurofunctional deficits seen as a result of inflammatory responses, and restore CD200 expression which is specific to IL-4 (Kiyota et al. 2010; Lyons et al. 2007a, b). Neuroinflammatory states have also been shown to greatly decrease neurogenesis in the SVZ and SGZ, which may explain the deficit in 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 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, 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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