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Microglia of the Aged Brain: Primed to be Activated and Resistant to Regulation

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Abstract

Innate immunity within the central nervous system (CNS) is primarily provided by resident microglia. Microglia are pivotal in immune surveillance and also facilitate the coordinated responses between the immune system and the brain. For example, microglia interpret and propagate inflammatory signals that are initiated in the periphery. This transient microglial activation helps mount the appropriate physiological and behavioral response following peripheral infection. With normal aging, however, microglia develop a more inflammatory phenotype. For instance, in several models of aging there are increased pro-inflammatory cytokines in the brain and increased expression of inflammatory receptors on microglia. This increased inflammatory status of microglia with aging is referred to as primed, reactive, or sensitized. A modest increase in the inflammatory profile of the CNS and altered microglial function in aging has behavioral and cognitive consequences. Nonetheless, there are major differences in microglial biology between young and old age when the immune system is challenged and microglia are activated. In this context, microglial activation is amplified and prolonged in the aged brain compared to adults. The cause of this amplified microglial activation may be related to impairments in several key regulatory systems with age that make it more difficult to resolve microglial activation. The consequences of impaired regulation and microglial hyper-activation following immune challenge are exaggerated neuroinflammation, sickness behavior, depressive-like behavior and cognitive deficits. Therefore the purpose of this review is to discuss the current understanding of age-associated microglial priming, consequences of priming and reactivity, and the impairments in regulatory systems that may underlie these age-related deficits.

Keywords

Brain; Microglia; Aging; Inflammation; Behavior

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Competing interests

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Increased inflammatory status in the aging brain

There is significant clinical and experimental evidence that inflammation within the central nervous system (CNS) increases with age. A hallmark of brain aging is increased oxidative stress and lipid peroxidation. Therefore, one hypothesis is that the accumulation of free radical damage over time leads to increased inflammation within the brain. Consistent with this premise, a myriad of microarray studies indicate that there is an overall increase in inflammatory and pro-oxidant genes while there is a reduction in growth and anti-oxidant genes in the brain of older rodents compared to adults (1, 2). Moreover, there are increased protein levels of several inflammatory cytokines, including interleukin (IL)-1β and IL-6, in the brain of aged rodents (2–8). In addition, there are reductions in several anti-inflammatory cytokines including IL-10 and IL-4 (9–12). There is significant interest in understanding why there is an age associated shift in the inflammatory profile of the brain. Recent evidence indicates that the resident glia are key contributors to the increased inflammatory state of the CNS.

Microglia

The majority of aging research focuses on understanding how age influences microglia biology. This is because microglia are dynamic cells of the CNS that play pivotal roles in development, plasticity and immune surveillance (for reviews see (13, 14)). During homeostasis, microglia perform essential functions including monitoring synapses (15), clearing up apoptotic debris (16, 17) and are involved in synaptic pruning (18). Surveying microglia have a ramified morphology with long and thin processes. These processes are highly motile and continuously survey the local microenvironment. The continuous sampling of the microenvironment ensures that microglia will quickly respond to any local disturbances in homeostasis (19, 20).

The distribution of microglia throughout the brain is diverse and varies amongst species. In humans, microglia comprise up to 16 % of the CNS cellular population and this is dependent on brain region. For instance, microglia are present at a higher density in white matter than gray matter in humans (Mittelbronn et al., 2001). In rodents, microglia comprise between 5–12 % of the CNS cellular population. Microglia in the rodent brain, however, are found at a higher density in the gray matter compared to white matter (21, 22).

Because of their similarity to macrophages, microglia are referred to as the resident innate immune cells of the CNS. This is because they can provide several macrophage related activities that provide an innate immunity as the first and main form of active immune defense in the brain. Consistent with these functional similarities to macrophages, microglia are derived from primitive yolk-sac myeloid cells and migrate to the CNS during embryonic development (23, 24). Once microglia reach a final differentiated state in the brain, microglia replication is limited. However, several studies report that microglia proliferate after traumatic CNS injury (25, 26). The effect of aging alone on microglial replication is controversial with the general consensus that there is not an increased number of microglia with age (27). The turnover of parenchymal microglia from bone marrow is also limited (28). For example, a recent study showed that microglia turnover from bone marrow derived myeloid cells ranged between nonexistent to 10 % over a 12 month period that microglial turnover was determined (24). Moreover, other studies examining myeloid cell trafficking in the context of CNS pathology indicate that self-renewal of microglia is likely from a CNS derived progenitor source, rather than from bone-marrow derived cells (29, 30). This is in contrast to CNS perivascular and meningeal macrophages that are renewed every 3–4 weeks from bone marrow derived circulating monocytes (31, 32). The limited replication and turnover of microglia make them a relatively stable population that is maintained throughout

life. Therefore, aging is likely to have a profound effect on this relatively stable population of resident microglia.

Microglia are key mediators of the coordinated response to infection by the peripheral immune system and CNS. Microglia respond to and propagate inflammatory signals initiated at the periphery. Following activation, microglia produce pro-inflammatory cytokines including IL-1β, IL-6, and tumor necrosis factor alpha (TNFα) (14). These cytokines are essential for the induction and maintenance of the behavioral symptoms of sickness (reviewed by, (33)). These cytokines also promote the release of secondary inflammatory mediators including prostaglandins and nitric oxide (34–36). The activation of microglia and the production of cytokines is transient and microglia return to a surveying state as the immune stimulus is resolved.

Evidence of microglial priming in the aged brain

The increased inflammatory profile of the CNS with age is associated with microglial priming (Fig. 1). For example, there is increased expression of inflammatory markers including MHC II and complement receptor 3 (CD11b) in the aged brain of humans, rodents, canines, and non-human primates (2, 9, 27, 37–44). Many of these markers are present specifically on microglia of the aged brain, including MHC II (44). MHC II is relevant because it is conserved across species and is interpreted to indicate microglial priming. For example, approximately 25% of microglia from aged mice were MHC II positive, compared to only 2% of microglia from adult mice (44). Consistent with microglial priming, other inflammatory markers are also increased in models of aging. These include scavenger receptor CD68 (2, 45), CD11b and CD11c integrins (37, 46), Toll-like receptors (TLR) (27, 47), and co-stimulatory molecule CD86 (B7) (48) (Fig. 1).

Consistent with the increased inflammatory profile of microglia there is also evidence of an activated morphology in the brain of aged. Staining microglia against ionized calcium-binding adaptor protein-1 (Iba1), a protein expressed on the surface of microglia, indicate that microglia from non-diseased healthy brains in aged dogs, gerbils, and mice have shorter and less branched dendritic arbors than young adults (49, 50) (Fig. 1). This de-ramified morphology is comparable to the activated morphology of microglia. Moreover, a recent study showed that the de-ramified morphology of microglia in aged rats corresponded with higher protein expression of MHC II (27). These data are consistent with the hypothesis that MHC II is a marker for primed microglia. In addition, the higher inflammatory profile of microglia in the aged is also associated with a moderate increase in mRNA expression of pro-inflammatory cytokines TNFα, IL-1β and IL-6 (7). Not only were pro-inflammatory cytokine expression increased in this population but anti-inflammatory IL-10 and transforming growth factor beta (TGFβ) expression were also increased in aged microglia. Taken together, the increase in microglial associated mRNA and protein of inflammatory mediators indicates that they have a more primed, or inflammatory phenotype.

Astrocytes also have a more inflammatory profile with age

As described above, the majority of aging studies examine the effect of age on microglia. It is important, however, to briefly discuss that astrocytes become more inflammatory with age. For instance, there is increased expression of astrocytic glial fibrillary acidic protein (GFAP) in the brain of aged rodents and humans (2, 27, 51–54). In addition, vimentin, an intermediate filament protein, also increases with aging in humans (55). Furthermore, there is an increased hypertrophic morphology of hippocampal astrocytes with a shift from resting/stellate to activate in the brain of aged rats (27). The age related increases in GFAP and vimentin are similar to the activated astrocytic profile associated with inflammation and

traumatic CNS injury (56, 57). Overall, these experimental and clinical data indicate that astrocytes have a more inflammatory profile with age.

There are many potential consequences of a more inflammatory astrocyte in the aged brain. First, astrocytes communicate directly with neurons and microglia, so an inflammatory astrocyte phenotype may directly effect immune to brain communication and microglia regulation (58). Second, astrocytes are integral to maintaining an intact blood brain barrier (BBB) (59). Age-related changes in astrocytes can affect BBB permeability, especially under inflammatory conditions and neurodegenerative diseases (60, 61). For example, Alzheimer's disease is associated with increased occurrence of amyloid-β peptides that enter the brain from the periphery. Third, astrocytes secrete cytokines and chemokines that can function to recruit peripheral immune cells to the brain. For example, transforming growth factor (TGF) β1 signaling in the brain stimulates astrocytes to increase expression of MCP-1 (CCL2) (62), which is a key chemokine involved in the recruitment of peripheral monocytes. In fact, a recent report indicated that increased TGFβ signaling was detected in aged mice compared to adults with increased phosphorylated-Smad2 (63). Because TGFβ increases GFAP expression during differentiation (64), this may explain increased GFAP expression on astrocytes of the aged brain. Overall, astrocytes become more inflammatory with age, but the reasons why this shift in phenotype occurs or the potential consequences are unknown.

Increased inflammation within the aged brain influences cognition and neuronal plasticity

A modest increase in the inflammatory profile of the CNS in aging is associated with deficits in motor coordination, cognition and neuronal plasiticity. For example, aged mice had psychomotor deficits in psychomotor coordination and balance tests including rod walking and plank walking (65, 66). These deficits were associated with increased *ex vivo* IL-6 production and lipid peroxidation in the brain. Aged mice fed an antioxidant rich diet had reduced IL-6 *ex vivo* production that was associated with improved motor coordination (65).

Several studies report cognitive deficits associated with age. For instance, aged mice tested in the Morris water maze had learning/acquisition impairments compared to adult mice (67). In addition, another study reported age-associated memory impairments in the reversal task of the Morris water maze (68). Lowering CNS inflammation by treating with the anti-inflammatory agent luteolin resulted in better performance in the Morris water maze (68). Other tasks for cognition have given similar results. For example, in both the contextual fear conditioning test and radial arm maze, aged mice had memory impairments when compared to adult mice (69). It is important to point out, however, that not all aged mice perform poorly in memory tasks. One study found that performance in the Morris water maze varies by the individual rat and that not all aged rats showed learning deficits compared to adult rats (27). In addition, when aged rats were grouped into cognitive intact and cognitive impaired subsets, there was no correlation between baseline glial activation and cognitive impairment (27). Therefore, the mechanism for the development of impaired cognition remains unclear. Overall, there is variability associated with aging and cognitive impairments but all the studies discussed above indicate that aging is a risk factor for cognitive impairment.

These age-related deficits in cognition may be related to reductions neuronal plasticity. For instance, increased neuroinflammation with age has negative effects on neurogenesis, dendritic restructuring and long term potentiation (LTP). These are all important for cognitive function and establishment of memories. Impairments in both neurogenesis and

LTP are reported in models of aging. For example, neurogenesis steadily decreases throughout life in mouse models of aging (70, 71). In an extensive study, reduced regenerative capacity indicative of senescence was reported in the mouse forebrain. There reductions were associated with declines in neuronal progenitor proliferation in the subventricular zone, neurogenesis in the olfactory bulb, and self-renewal potential (72). Moreover, additional reports of declined neurogenesis with age were associated with impairments in both the contextual fear conditioning test and radial arm maze (69). The increased amount of pro-inflammatory cytokines and oxidative stress present in the aged brain also has negative effects on LTP. Specifically, high IL-1β concentrations decrease LTP sustainability (73–76) and increased oxidative stress present in the aged reduced LTP (66). The correlation between increased neuroinflammation with age and reduced LTP is indicated by several reports (5, 48). For example, LTP was impaired in 9 and 15 month old rats and these ages corresponded with increases in brain levels of IL-1β and interferon gamma (IFNγ) (48). Lowering hippocampal IL-1β by minocycline treatment partially rescued this impairment in LTP (48), indicating that lowering inflammation by inhibiting microglial activity has beneficial effects on LPT. In similar studies, the anti-inflammatory agent rosiglitazone also restored LTP in aged rats (77, 78). Rosiglitazone, however, lowered the activation profile of astrocytes (decreased GFAP, decreased RANTES, and decreased TNF-α response in vitro), and not microglia, highlighting astrocytes as important CNS immune cells (78).

In addition to increased IL-1β and oxidative stress, decreases in neurotrophins also negatively impact LTP. Specifically, brain-derived neurotrophic factor (BDNF) is important for consolidation of hippocampus-dependent memory and maintaining LTP (79–81). This has implications for aging because decreased levels of BDNF transcripts and protein were found in the CA1 and CA3 regions of the hippocampus in aged rats (82–84). Overall, the increased inflammatory status of the brain and the decrease in neurotrophic support both contribute to decreased LTP and can result in impaired hippocampal dependent memory.

There is increasing evidence that cognition, neurogenesis, and LTP are influenced by peripheral growth factors. This is supported by studies using exercise to modulate the CNS environment. Exercise increases angiogenesis and thus provides more blood vessels and supporting endothelial cells for neurogenic niches to be formed (85). In aged mice, exercise enhanced learning, memory, and neurogenesis (71). These beneficial effects of exercise on the activity of neural progenitor cells and on cognitive impairments has been replicated by other groups (86–88), however, the mechanisms and pathways underlying these effects are still speculative. More recent reports showed that microglia have an important role in relaying the systemic effects of exercise to the CNS by providing a proneurogenic environment (89, 90). For example, microglia isolated from exercised animals were able to induce neurosphere formation *in vitro*. Furthermore, fractalkine receptor deficient microglia and microglia from aged mice had negative effects on neurosphere formation. This study indicates that microglia can exert dual roles on neural progenitor cell activity depending on their inflammatory state (89).

Furthermore, there is additional evidence that plasma derived factors has implications for brain aging. A recent article reports that plasma from young mice can ameliorate the decline seen in neural progenitor cells and neurogenesis in aged mice (69). This study used a parabiosis model in which two mice shared circulation. Aged mice paired with young mice showed improved memory as assessed by the fear conditioning test and an increase in neurogenesis and neural progenitor cells. Similarly, young mice sharing aged blood showed a decline in neurogenesis and number of neural progenitor cells. The authors then continued by attempting to pin-point the blood-born factors responsible to the impairments in aged

mice. Their analysis reveled several chemokines, most significantly CCL11, believed to be the determinants in inhibiting neurogenesis (69).

Behavioral and cognitive consequences of impaired coordination between the immune system and the brain

Innate immune challenge leads to prolonged and exaggerated neuroinflammation

While aging alone reduces neuronal plasticity, major differences in microglial biology between young and old age occur when the immune system is challenged and microglia are activated. Thus, the increased markers of inflammation observed on microglia and astrocytes in the aged brain sets the stage for an increased or exaggerated immune response following stimulation. In support of this idea, exaggerated neuroinflammation in aging models has been reported following both peripheral and central immune activation (for reviews see (91–93)). For example, mixed glial cultures and coronal brain sections from aged mice produced elevated levels of IL-1β and IL-6 following lipopolysaccharide (LPS) stimulation compared to those established from adult mice (4, 10). LPS is a component of gram negative bacterial cell wall and is a potent activator of the innate immune system. *In vivo*, peripheral injection of LPS or *E. coli* caused prolonged and exaggerated neuroinflammation associated with increased IL-1β and IL-6 in aged rodents compared to young adults (2, 94). Similarly, central injection of LPS or GP120 caused amplified mRNA expression of IL-1β, IL-6 and TNFα in aged mice (95, 96). The increased expression of IL-6 mRNA was mirrored with enhanced IL-6 signaling in the aged brain after LPS injection (97). In addition, elevated mRNA expression of IL-1β, TNFα, and the inflammatory associated enzyme indoleamine 2,3-dioxygenase (IDO) was detected 24 and 72 h after LPS injection (84, 98), indicating that the neuroinflammation is both exaggerated and prolonged in the aged brain.

Several studies indicate that this exaggerated cytokine production is dependent on activation of microglia. For example, pretreatment with minocycline, an anti-inflammatory agent and reported microglial inhibitor (99, 100) attenuated the LPS induced amplification of TLR2, IL-1β, IL-6 and IDO in the hippocampus of aged mice (101). Moreover, a recent study showed that MHC II positive microglia were responsible for the robust increase of IL-1β following inter-peritoneal (i.p) injection of LPS. In this study, microglia were isolated from adult and aged mice 4 hours following LPS injection and analyzed by flow cytometry for intracellular IL-1β production. While LPS treated adult and aged mice exhibited a similar percentage of MHC II negative microglia expressing IL-1β, LPS treated aged mice had a significant increase in MHC II positive microglia expressing IL-1β. Furthermore, additional analysis of microglia from aged mice indicated that 95% of MHC II positive microglia were IL-1β positive, whereas only 31% of MHC II negative microglia were positive for IL-1β. These data support the hypothesis that primed MHC II positive microglia are highly responsive to immune challenge and provides a direct connection between heightened neuroinflammation and microglia. When microglia were isolated as a single population, other studies have reported similar age effects on microglial cytokine expression profile. Microglia isolated from aged mice 4 hours after LPS injection had increased mRNA levels of IL-1β, TLR2 and IDO compared to adult mice injected with LPS (44). In a similar study, elevated expression of TNFα, IL-1β, IL-6, and IL-12 mRNA were reported in aged LPS injected mice compared to adults (7). Other related studies indicated that microglia from aged mice stimulated *ex vivo* with LPS and Pam3CSK4, a TLR2 agonist, produced higher levels of IL-6 and TNFα than microglia from young mice (102). Overall, these studies indicate that immune challenge in the aged leads to exaggerated pro-inflammatory cytokine production by microgila (Fig. 2).

Microglia activated by an innate immune challenge are also activated for a longer duration in the aged brain compared to adults. This results in a protracted production of inflammatory cytokines. For example, exaggerated microglial expression of IL-1β was continued up to 24 h after LPS injection in aged mice (103). Furthermore, elevated expression of hippocampal IL-1β has been reported for up to 72 h following LPS injection (84). This prolonged upregulation of inflammatory cytokines may be related to an impaired ability to "shut off" active microglia. In support of this notion, activated microglia from aged mice actually had higher levels of IL-10 production than those of adult mice (7, 44) and lower expression of TGFβ (7). IL-10 is an anti-inflammatory cytokine and can regulate IL-1β production. Thus, increased IL-10 but a maintained inflammatory response could imply that the aged brain has an impaired response to IL-10.

Primed microglia in the aged brain also produce a more robust response to peripheral stimulation induced by injury and stress. For example, minor abdominal surgery resulted in neuroinflammation and increased IL-1β levels 24 h post surgery in aged, but not adult mice (67) and mild psychological stress induced an amplified central cytokine response with increased IL-1β mRNA and MHC II protein expression in the hippocampus of aged but not adult mice (104). Overall, neuroinflammation is exaggerated in aged animals following central or peripheral stimulation, and many of these changes can be attributed to a hyperactive and primed microglial population.

It is also important to mention that microglial priming is detected in other models including neurodegenerative disease (for review see (105)). For example, both prion diseases (transmissible spongiform encephalopathies) and Alzheimer's Disease show marked astrocyte and microglial activation (106–108), and evidence of microglial priming is apparent in both of these models of neurodegeneration. For example, in a murine model of pre-clinical prion disease, both central and peripheral inflammation exacerbated brain inflammation and neuronal death in prion disease mice compared to controls (109). This study was the first to demonstrate microglial priming under pre-symptomatic conditions as LPS challenge caused a marked increase in IL-1β and inducible nitric oxide synthase (iNOS) expression in microglia of prion disease mice compared to control mice (109). In a similar manner, microglial priming was also detected in transgenic mouse models of Alzheimer's disease. In these models, systemic challenge with LPS caused a significant increase in CNS inflammation with exacerbated IL-1β and iNOS compared to non-transgenic controls (110, 111). The priming of microglia and their hyperactivation under pro-inflammatory conditions may contribute to or even amplify the neurodegenerative processes of prion and Alzheimer's disease, making microglial priming an important research focus in the field of neurodegeneration. Overall, there are many examples of microglial priming in various models, but the focus on this review is on microglial priming under non-pathological conditions.

We refer to microglia of the aged brain as a primed or reactive microglial population. This is because they express increased markers of inflammation and when activated by an innate immune challenge (i.e., LPS) they have an amplified activation profile. Nonetheless, others described microglia of the aged brain as senescent or dystrophic (112). The terminology used depends on the context in which the microglia are examined and it is clear that microglia from older rodents also have other functional impairments. For example, there was reduced phagocytosis of beta-amyloid by microglia from older AD transgenic mice (113, 114). Microglia from aged rats showed delayed recruitment of phagocytic cells and less clearance of myelin after a toxin-induced demyelination lesion (115). In addition, in a focal laser injury model microglia from aged mice migrated at a slower velocity towards the site of injury and also aggregated at the injury site for a longer duration than that of adult mice (116). These functional impairments may be considered indicators of microglial

senescence. Therefore the terminology of microglial priming or microglial senescence both reflect age-related differences in microglia function, but are related to the context in which they are examined.

Sickness and depressive-complications following innate immune challenge

As discussed above, inflammatory challenge in the elderly leads to exaggerated and prolonged inflammation in the brain. Prolonged exposure to cytokines such as IL-1β and IL-6 is accompanied by behavioral complications including prolonged sickness response, depression, and cognitive impairments (93). For example, our lab and others have shown that central and peripheral LPS challenge in aged mice caused prolonged and exaggerated sickness response characterized by protracted anorexia, lethargy, and social withdrawal (2, 95, 96) (Fig. 2). Aged rats also displayed an altered febrile response to *E. coli* infection. The aged rats had a delayed increase in core body temperature but this was followed by a significant and prolonged increase lasting up to three days (117). The exaggerated sickness response was likely caused by the exaggerated and prolonged production of IL-1β by MCH II positive microglia in aged mice (44) because a central administration of an IL-1 receptor antagonist rescued the behavior (118).

In addition to a prolonged sickness response, aged mice also developed depressive-like behavior following immune challenge (Fig. 2). To evaluate the depressive state of rodents, resignation behavior is determined in the trail suspension test (TST) and forced swim test (FST). Protracted depressive like behavior in the TST and FST were evident in aged mice 72 h after injection of LPS but not in adult mice (98). It is important to note that the depressive behavior was independent of general lethargy associated with the sickness response (98). These findings in animal models are consistent with clinical findings in which elderly patients exposed to infection or illness have an increased frequency of behavioral complications including depression and delirium compared to younger adults with similar peripheral insults (119). One potential reason for exaggerated depression after LPS injection in aged mice is heightened activation of the IDO pathway. IDO is an important enzyme in the degradation of tryptophan. This is important because inflammation-associated depression results from tryptophan degradation into kynurenine and subsequent monoamines which leads to the development of neuroactive metabolites and an imbalance in glutamate and serotonin neurotransmission (for reviews see (120, 121)). In comparisons between young and old mice, LPS caused a prolonged depressive phenotype that was not apparent in the adult matched controls. This depression was associated with increased inflammatory cytokine production in the brain, IDO upregulation, and serotonin turnover (98). In addition, microglia from aged mice injected with LPS had an exaggerated upregulation of IDO mRNA (44). Therefore a hyperactive microglial response with amplified IDO expression may underlie the prolonged depressive-like behavior in aged mice after peripheral LPS injection (98). In support of the role of IDO in inflammatory mediated depression, recent studies indicate that inhibiting IDO with 1-methyl tryptophan blocks development of inflammatory induced depression in adult mice (122, 123).

Cognitive impairments

There are also cognitive consequences of an exaggerated response to peripheral or central immune challenge. As discussed previously, aging alone is associated with some memory impairments. Following an immune challenge, however, cognitive impairments are exaggerated and become more apparent in the aged. These impairments are likely linked to increases in IL-6 and IL-1β because high levels of CNS IL-6 can inhibit memory formation and learning, cause neurodegeneration and exacerbate sickness behavior (124). These effects are similar to that of IL-1β as high IL-1β concentrations in the hippocampus are associated with impaired memory (125–127). For example, LPS injection in aged mice caused an

amplified cytokine response in the hippocampus and this was paralleled by learning deficits in the radial arm water maze (128) and memory consolidation deficits in contextual fear conditioning (97). By inhibiting IL-6 signaling using an antagonist, contextual fear conditioning impairments were rescued in aged mice (97). Similar to aged mice, aged rats also had reduced long-term contextual memory in the contextual fear conditioning test and the Morris water maze following *E. coli* infection (94, 129). The anti-inflammatory agent resveratrol had beneficial effects on cognition in aged mice (130). In this study, mice received resveratrol supplemented in their diet and following LPS injection they were tested in the Morris water maze. Resveratrol lowered plasma and hippocampal IL-1β and this reduction in inflammation was paralleled by an attenuation of the memory deficits in aged mice (130).

Similar to the effects of inflammation on cognition, an exaggerated response in the aged brain may also impair cognition through impaired neuronal plasticity. For example, peripheral LPS injection caused amplified inflammation that lead to increased dendritic atrophy in the CA1 region of the hippocampus in aged mice (84). Adding to the effects of increased CNS inflammation, BDNF mRNA decreased following *E. coli* or LPS injection (82, 84). This decrease in BDNF was even more pronounced in aged rats that already had reduced baseline levels BDNF transcripts, making aged rats more prone to the behavioral deficits caused by decreased BDNF following injection (82, 84). Furthermore, the effects of inflammation on LTP sustainability also becomes apparent in aged rodents. For example, aged, but not adult, rats challenged with *E. coli* showed late phase LTP deficits and impaired hippocampal dependent memory (131). Furthermore, these impairments were rescued by central administration of the anti-inflammatory cytokine IL-1 receptor antagonists which blocks IL-1β signaling (131, 132). In a similar study, amyloid-β challenge inhibited LTP in aged but not adult rats (133). In summary, microglia from aged animals are primed and have an exaggerated immune response following activation which leads to heightened inflammation in the brain and reductions in LTP.

Impaired regulation of microglia in the aged brain

The cause of this amplified microglial activation with age may be related to impairments in several key regulatory systems that make it more difficult to resolve microglial activation (Fig. 3). Microglial activity can be modulated by anti-inflammatory cytokines including IL-10, TGFβ and IL-4. Although IL-10 was decreased in the brain of aged rodents under homeostatic conditions, following immune challenge, IL-10 levels were exaggerated in aged microglia compared to adults (44). IL-10 is a potent anti-inflammatory cytokine that should regulate IL-1β production and decrease inflammation. It is unclear why higher IL-10 is ineffective in reducing brain inflammation after LPS challenge in older mice. Microglia, however, do not express high levels of IL-10 receptor and do not appear to respond to the M2 promoting effects of IL-10 (134). Similar to IL-10, TGFβ is an anti-inflammatory factor that can regulate microglia (135). For example, TGFβ increases fractalkine receptor expression and reduces IL-1β mRNA in BV2 microglia stimulated with LPS (103). In adult mice, TGFβ mRNA increased in the brain 24 after LPS injection, however, this increase was not detected in aged mice (103). This lack of TGFβ mRNA induction following inflammatory challenge can therefore be a possible link to the prolonged microglial activation reported in aged mice. Taken together, deficits in IL-10 and TGFβ signaling pathways with age may lead to a reduced ability to shut off microglia.

IL-4 is another anti-inflammatory cytokine that is influenced by age. For example, in aged rats there was reduced IL-4 levels in the brain and this corresponded with increased neuroinflammation and reduced LTP (11, 12). Induction of hippocampal IL-4 successfully restored LTP in the aged rats (136) suggesting an important role for IL-4 to modulate the

CNS environment and retain LTP by lowering CNS inflammation. Similarly, IL-4 attenuated neuroinflammation and restored LTP in adult rats challenged with amyloid-β protein (137). In addition to reductions in IL-4 with age, there are also reductions in IL-4 sensitivity with age. For instance, recent work indicates that microglia from the brain of aged mice were less responsive to the anti-inflammatory effects of IL-4 (134). Following peripheral LPS stimulation, microglia from adult but not aged mice had upregulated expression of IL-4 receptor-alpha (Fig. 3). After isolation, microglia were stimulated with IL-4 *ex vivo.* Microglia from adult mice were responsive to IL-4 and shifted in phenotype towards an alternatively activated M2 state whereas microglia from aged mice retained a classically activated or M1 phenotype in the presence of IL-4 (134). Therefore, the failure to upregulate IL-4 receptor on microglia of aged mice was associated with decreased sensitivity to IL-4. Taken together, either reduced levels of IL-4 or a reduced sensitivity IL-4 in the aged brain impairs the ability to lower inflammation in the brain. This is potentially important because IL-4 has a role in maintaining memory and learning (138) and reparative processes after traumatic CNS injury (139).

In addition to regulation by anti-inflammatory cytokines, microglia are also regulated by neuronally derived proteins including fractalkine, CD200, and TREM2. These regulatory systems are important to keep microglia in a surveying state (reviewed by (13, 105). For example, fractalkine signaling is important for maintaining microglia in a resting state and also attenuating microglial activation following the removal of inflammatory stimulus. Neuronally expressed fractalkine ligand (CX_3CL) can exist as either membrane bound or released as a free ligand. Both forms of fractalkine bind to the corresponding fractalkine receptor (CX_3CR) which is expressed exclusively on microglia in the CNS. *In vitro*, the addition of fractalkine ligand to LPS stimulated glia cultures attenuated production of inflammatory mediators including IL-1β, IL-6, TNFα, inducible nitric oxide synthase (iNOS), and MHC II (140–142). The importance of fractalkine signaling is mirrored *in vivo* by transgenic fractalkine receptor knockout mice where microglial activity is dysregulated. Following peripheral LPS stimulation, fractalkine receptor knockout mice had amplified IL-1β production in the brain (143, 144) and amplified microglial expression of IL-1β, and the inflammatory associated enzymes IDO and kynurenine 3-monooxygenase (KMO) at 4 h after injection and prolonged induction of IL-1β, TLR2 and CD14 24 h after injection compared to heterozygote controls (144). The increased expression of IDO and KMO in microglia from fractalkine receptor knockout mice was associated with prolonged depressive like behavior following peripheral LPS challenge compared to wild-type and heterozygote mice (144). Blocking IDO activity in these mice blocked the development of depressive-like behavior (145) suggesting IDO is important for the development of depression in models where microglial regulation is impaired. Overall, these results indicate that fractalkine signaling is important to modulate the microglial response following activation and also returning microglia to homeostasis following cease of inflammation.

Fractalkine signaling has implications in aging because several studies indicate that fractalkine ligand was lower in the aged brain compared adult (89, 103, 142, 146). In addition, following LPS challenge, microglia from aged mice showed prolonged downregulation of the fractalkine receptor (103). In this study by Wynne et al., microglia from both adult and aged mice had downregulated fractalkine receptor at 4 h following LPS injection. Microglia from adult mice, however, had restored levels of fractalkine receptor at 24 h but this was not observed in microglia from aged mice. This failure to upregulate the receptor by 24 h corresponded with prolonged induction of IL-1β and an extended sickness response. Taken together, reduced levels of fractalkine ligand and prolonged downregulation of fractalkine receptor can combine to give severe impairments in fractalkine signaling in the aged brain, which ultimately leads to a dysregulated microglial population (Fig. 3).

Similar to fractalkine, CD200 regulation keeps microglia in a resting state and this regulation is also impaired in the aged brain. CD200 is membrane glycoprotein expressed on neurons and oligodendrocytes. The CD200 receptor (CD200R) is expressed exclusively on microglia and the binding of CD200 ligand to CD200R plays a pivotal role of modulating microglial activation (147, 148). For example, CD200-deficient mice show a greater extent of microglial activation in several models of inflammation (147, 149). Following a peripheral injection of LPS, microglia downregulated CD200R and this downregulation was associated with an increase in microglial activation (150). This is relevant because in aged rats, there was less CD200R mRNA and protein expression on microglia (9, 148) compared to adult rats. In addition, there are decreased levels of CD200 in aged rats compared to adults (148, 151) (Fig. 3). Enhancing CD200 signaling by injection of a mimetic of the neural cell adhesion molecule (NCAM) FGL or CD200 fusion protein rescued some of the age-related phenotypes. For example, FGL attenuated expression of pro-inflammatory cytokines in the brain following LPS injection in aged mice (152). In a similar manner, intrahippocampal injection of CD200 fusion protein decreased microglial activation in the hippocampus of aged rats, and this decrease in activation correlated with rescued LTP, which was impaired following LPS injection in aged rats (151). In addition, systemic treatment with FGL had positive effects on glial-synaptic interactions (153) which were also otherwise impaired in aged rats. These findings indicate that CD200 signaling is important for modulating microglial activity, and impairments in CD200 with age can have detrimental effects on microglia to neuron interactions.

Conclusions

In conclusion, there are inflammatory alterations in microglia biology with aging. Microglia of the aged brain are termed primed with a higher expression of MHC II and pro-inflammatory cytokines including IL-1β. This shift towards priming is associated with a prolonged and amplified response to an immune challenge. In addition, there are clear age associated deficits in memory and learning and neuronal plasticity. These deficits can worsen by inflammatory challenge. Aging is also associated with dysregulation of microglia, for example deficits in CD200 and fractalkine regulation. What causes these impairments and gives rise to a primed microglial population, however, remains to be elucidated. Therefore, a better understanding of the pathways by which microglia become dysregulated with age is needed to improve our understanding of neuroinflammatory complications associated with age and lead to the development of therapeutic interventions.

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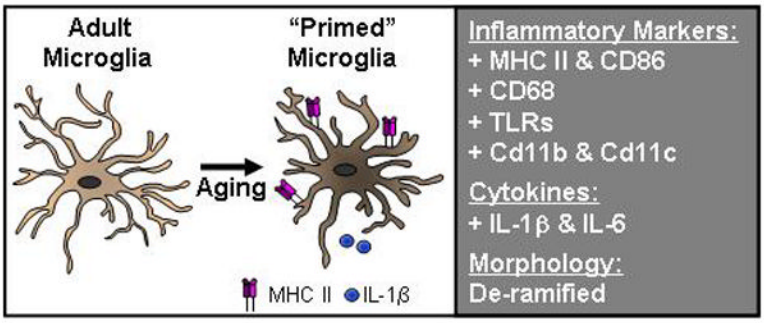


Figure 1. Evidence of microglial priming in the aged brain

In normal aging there is increased mRNA and protein expression of several inflammatory markers on microglia. In older rodents and non-human primates these include proteins associated with antigen presentation, (MHC II and CD86), scavenger receptors (CD68), pattern associated recognition receptors (Toll-like receptors), and integrins (CD11b and CD11c). There are also detectable increases in inflammatory cytokines and decreases in anti-inflammatory cytokines in the aged brain. Last, in several aging models the morphology of the microglia is more de-ramifed. Collectively these findings are interpreted to indicate that microglia of the aged brain maintain a primed or activated immune profile.

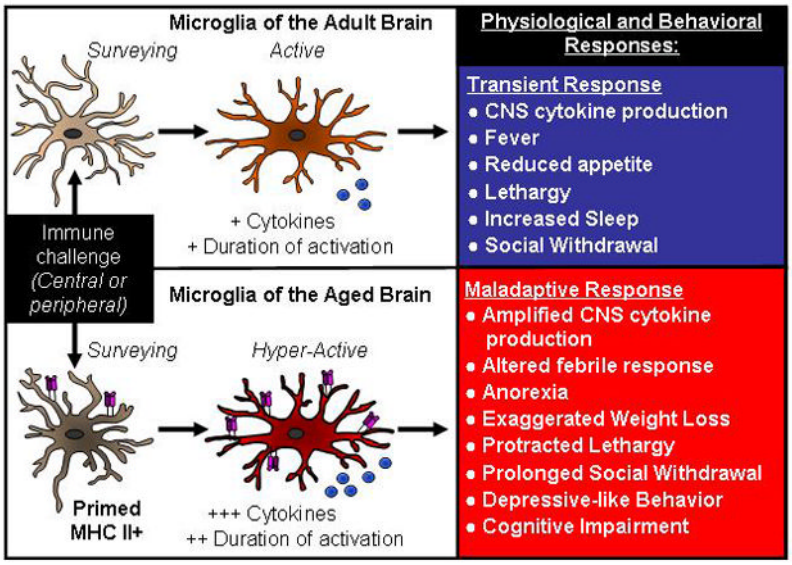
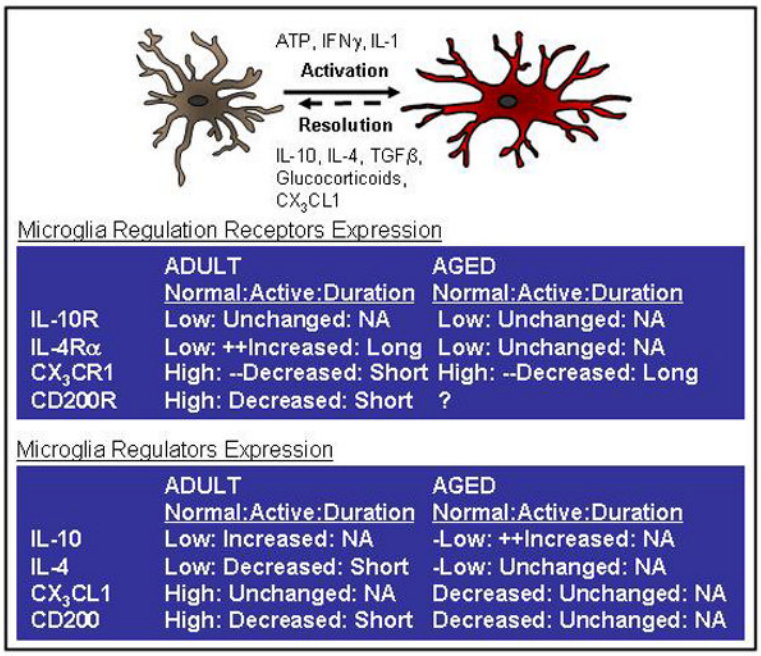


Figure 2. Neurobehavioral complications associated with microglial reactivity in the brain of aged

Under normal conditions, microglia interpret and propagate inflammatory signals that are initiated either peripherally or centrally. Microglial activation increase cytokine and secondary messenger release that lead to transient physiological and behavioral responses that are beneficial to the host organism (top panel). A consequence of microglial priming with age, however, is a hyperactive response to an immune challenge with amplified and prolonged production of cytokines. In several models of aging, an exaggerated cytokine response is associated with the development of cognitive, behavioral, and physiological complications that are interpreted to be maladaptive to the host organism (bottom panel).



Microglia Regulation Receptors Expression

	ADULT Normal:Active:Duration	AGED Normal:Active:Duration
IL-10R	Low: Unchanged: NA	Low: Unchanged: NA
IL-4Rα	Low: ++Increased: Long	Low: Unchanged: NA
CX_3CR1	High: --Decreased: Short	High: --Decreased: Long
CD200R	High: Decreased: Short	?

Microglia Regulators Expression

	ADULT Normal:Active:Duration	AGED Normal:Active:Duration
IL-10	Low: Increased: NA	-Low: ++Increased: NA
IL-4	Low: Decreased: Short	-Low: Unchanged: NA
CX_3CL1	High: Unchanged: NA	Decreased: Unchanged: NA
CD200	High: Decreased: Short	Decreased: Unchanged: NA

Figure 3. Activated microglia from the aged brain are refractory to anti-inflammatory stimulus

The activation of microglia is tightly regulated and there are several anti-inflammatory mediators that modulate microglial activation. For example, anti-inflammatory cytokines including IL-10, TGF-β, and IL-4 modulate the activation of microglia and are decreased in the brain with age. In addition neuronally derived ligands including CD200 and fractalkine (CX3CL1) are also decreased with age. The right panels depict the differences in expression of several regulatory proteins and receptors with age. There are also several regulatory systems in that the ligand and the receptor interaction that change when microglia become activated. For example, compared to adult microglia, aged microglia have prolonged reduction of CX3CR1 and fail to increase surface expression of the IL-4 receptor-α (bottom left panel). Taken together, the prolonged activation of microglia of the aged brain may be because they are less sensitive to the anti-inflammatory regulation that normally helps to resolve activation.