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Microglia, Lifestyle Stress, and Neurodegeneration

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Abstract

Recent years have witnessed a revolution in our understanding of microglia biology, including their major role in the etiology and pathogenesis of neurodegenerative diseases. Technological advances have enabled the identification of microglial signatures in health and disease, including the development of new models to investigate and manipulate human microglia *in vivo* in the context of disease. In parallel, genetic association studies have identified several gene risk factors associated with Alzheimer's disease that are specifically or highly expressed by microglia in the central nervous system (CNS). Here, we discuss evidence for the effect of stress, diet, sleep patterns, physical activity, and microbiota composition on microglia biology and consider how lifestyle might influence an individual's predisposition to neurodegenerative diseases. We discuss how different lifestyles and environmental factors might regulate microglia, potentially leading to increased susceptibility to neurodegenerative disease, and we highlight the need to investigate the contribution of modern environmental factors on microglia modulation in neurodegeneration.

Microglia are the resident phagocytes of the innate immune system in the central nervous system (CNS). They are the first responders to neuroinflammation or damage and rapidly adapt their phenotype and functions in response to the brain milieu. They are important for several physiological functions, such as phagocytic activity and cytokine production, and they support other brain cells. New technological advances, including single-cell genomics, quantitative proteomics, and epigenetic studies, identified a role for the molecular and functional regulation of microglia in health and disease (Gosselin et al., 2014; Li et al., 2019; Masuda et al., 2019; Tay et al., 2018b). As an example, transforming growth factor β (TGF-β) and colony-stimulating factor 1 (CSF1) signaling, as well as other transcriptional factors including *Sall1*, *Mafb*, *Irf8*, and *Pu.1*, were identified as regulators of homeostatic microglia (Butovsky et al., 2014; Lund et al., 2018; Qin et al., 2018).

Neurodegeneration consists of age-related progressive loss and death of neuronal structures and functions in the CNS, leading to potential alterations of cognitive performance and dementia (Ramanan and Saykin, 2013). During neurodegeneration, microglia acquire neurodegenerative signatures, including those driven by Triggering receptor expressed on myeloid cells 2 (TREM2)-Apolipoprotein E (APOE) (Keren-Shaul et al., 2017; Krasemann

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et al., 2017). On the basis of these findings, human induced pluripotent stem cell (iPSC)-derived microglia were generated, allowing researchers to investigate the contribution of microglia-enriched risk genes to human disease. It also resulted in the development of novel humanized mouse models to study human microglia *in vivo* in the context of neurodegenerative disease.

Environmental factors such as chronic stress might influence microglia, which might in turn affect an individual's susceptibility to neurodegeneration, because microglial dysfunction is a potential risk factor for Alzheimer's disease (AD) development (Bisht et al., 2018; Katsumoto et al., 2018; Phan and Malkani, 2018). Stress during the perinatal period has also been linked to increases in cognitive deficits and psychiatric diseases later in life associated with neuroinflammation through potential alteration of microglial functions during development (Knuesel et al., 2014; Meyer and Hamel, 2014; Tay et al., 2018a). Dietary factors affect gut microbiota composition and modulate the immune system. Gut microbiota dysbiosis can regulate neuroinflammtion and microglia and has been associated with increases in the severity of neurodegeneration in animal models (Dodiya et al., 2019; Erny et al., 2015; Thion et al., 2018). Western diet has also been associated with an exacerbation of AD pathogenesis potentially through the alteration of microbiota (Drasar et al., 1973; Reddy et al., 1975; Wu et al., 2011). Therefore, diet intervention might be a promising approach for modulating disease predisposition and progression. Modern lifestyle is also associated with abnormal sleep patterns, which potentially promotes neurodegenerative functions of microglia (Bellesi et al., 2017; Wadhwa et al., 2017a; Wadhwa et al., 2017b). In this review, we discuss studies defining the mechanistic regulators and upstream molecular pathways that could be therapeutic targets to ameliorate the negative effects of lifestyle factors and their potential consequences on the brain. Altogether, recognition of the negative consequences resulting from certain lifestyles and the importance of microglia in the etiology and progression of AD might allow people to adopt different lifestyles to modulate their susceptibility to neurodegenerative disease, in addition to other treatments.

Chronic Stress and Microglial Dysregulation in Neurodegeneration: From Perinatal Stages to Aging

Suffering from chronic lifestyle stress during certain periods of life has become a common feature of modern societies. Chronic lifestyle stress and, in particular, psychosocial stress might confer a risk factor for late-onset AD (LOAD) and associated cognitive deficits. AD is characterized pathologically by the accumulation of phosphorylated tau and β-amyloid (Aβ) plaques. AD patients have been shown to present 83% increased cortisol levels in their cerebrospinal fluid (CSF) compared with healthy age-matched controls (Sapolsky et al., 1985; Swaab et al., 1994). Reactive gliosis, which consists of a range of molecular, morphological, and functional changes of glia in the CNS, and neuroinflammation are prominent hallmarks of AD (McGeer et al., 1987; Sarlus and Heneka, 2017). Microglia surround amyloid plaques in both human AD and animal models, although their role in disease progression is unclear (Sarlus and Heneka, 2017).

Several epidemiological and preclinical studies have shown that environmental factors might influence AD incidence (Qiu et al., 2009) (Figure 1). Individuals with a life-long history of stress are at higher risk for developing brain atrophy, cognitive deficits, and AD (Alkadhi, 2012; Gracia-García et al., 2015). Consistent with clinical studies, a retrospective study showed that aged primates stressed during early life presented significantly higher levels of Aβ plaque deposition and a reduction in synapse number compared with non-stressed primates (Merrill et al., 2011). Another study reported that restraint stress, or an unavoidable stress situation, elevates glucocorticoid hormones, which are key regulators of essential physiological functions in mammals, including the immune system (Smith and French, 1997). In rodent models of AD, chronic stress exacerbates neurodegeneration and cognitive impairments (Alkadhi and Tran, 2015; Carroll et al., 2011; Srivareerat et al., 2009) and increases Aβ accumulation and tau phosphorylation (Catania et al., 2009; Green et al., 2006; Joshi et al., 2012). Post-traumatic stress disorder (PTSD) is a neuropsychiatric disorder occurring in response to traumatic stress such as a dangerous or shocking event. A retrospective study of veterans showed that PTSD is associated with a higher risk of developing dementia (Yaffe et al., 2010), AD, and frontotemporal dementia (Bonanni et al., 2018). In addition, rodent models of PTSD present accelerated Aβ plaque formation and release (Rothman et al., 2012). Thus, chronic lifestyle stress is associated with increased vulnerability to neurodegenerative diseases along the lifespan. Frontal cortex and hippocampus are particularly vulnerable to the effects of stress. Interestingly, these regions are among the first regions to be affected in AD pathology. However, potentially common underlying mechanisms between stress and AD pathology have not yet been well characterized.

Neuroinflammation is a consequence of chronic stress and has been well characterized in AD. Epidemiological studies showed that PTSD is associated with immune system dysregulation (Hori and Kim, 2019). In particular, chronic psychosocial stress induces peripheral and CNS inflammation in the adult (Eidson et al., 2019). Restraint stress increased neuroinflammation, characterized by gliosis, and increased inflammatory gene transcription and lipid peroxidation independent of Aβ levels in an AD mouse model (Perez Nievas et al., 2011). Microglia are thought to play a pivotal role in AD pathology and plaque removal (Gandy and Heppner, 2013). Transcriptomic analyses have revealed a neurodegenerative signature termed MGnD (neurodegenerative microglia) or DAM (disease-associated microglia) in plaque-associated microglia from both human and mouse AD models (Kamphuis et al., 2016; Keren-Shaul et al., 2017; Krasemann et al., 2017; Yin et al., 2017) that was largely absent from microglia from non-plaque areas. This disease-associated signature includes upregulated expression of *Apoe*, *Axl*, *Clec7a*, *Itgax*, and *Lgals3*, forming a common core of neurodegenerative (Krasemann et al., 2017) and disease-associated transcriptomes demonstrated by several groups (Holtman et al., 2015; Keren-Shaul et al., 2017; Srinivasan et al., 2016). This core phenotype is characterized by the induction of genes related to APOE signaling and the suppression of TGF-b signaling in microglia associated with cellular damage and neurodegeneration. The MGnD and DAM phenotypes includes expression of chemokines that can facilitate recruitment of inflammatory monocytes and activation of astrocytes (Liddelow et al., 2017). Association of MGnD/DAM microglia with Aβ plaques is clear; however, major questions remain regarding their

potential protective or disease-promoting functions. Innate immune cells can be protective in AD by reducing accumulation of Aβ (Frenkel et al., 2008; Simard et al., 2006), which happens early in the disease. Microglia might also lose their ability to phagocytose Aβ as they age (Hickman et al., 2013; Streit and Xue, 2009) and become neurotoxic with increasing Aβ deposition (Sastre et al., 2006; Streit et al., 2004). Chronic lifestyle stress sensitizes microglia toward a primed phenotype and induces neuroinflammation in the adult brain (Ramirez et al., 2016; Wohleb et al., 2014). Thus, stress might compromise the supportive roles of microglia for neurons and synapses, leading to deteriorating cognitive functions during aging. Once stressed, microglia change their gross morphology toward a more amoeboid, de-ramified phenotype with shorter and thicker processes (Kreisel et al., 2014; Wohleb et al., 2014). A marker for phagocytic activity, CD68, is increased on microglia in chronically stressed mice associated with augmented phagocytosis (Lehmann et al., 2016). Acute stress increases the number of microglia (Lehmann et al., 2016), whereas chronic stress decreases it, largely in the hippocampus (Tong et al., 2017). Thus, the intensity and duration of microglial activation by stress are important features that might lead to different pathological outcomes (Stein et al., 2017). However, persistent microglial pro-inflammatory activation after long exposure to stress could exacerbate neuronal damages and amyloidosis already present in AD pathology (Heppner et al., 2015). The potential contribution of somatic mutations toward chronic activation of microglia in neurodegeneration has to be taken into consideration. Indeed, somatic mutations in the line-age of erythro-myeloid progenitors (EMPs), to which microglia belong, might drive late-onset neurodegeneration by leading to constant microglial nuclear factor κB (NF-κB) activation and resulting in neuronal loss (Mass et al., 2017).

During postnatal development, many environmental factors, transmitted via the mother-child interaction, can affect proper brain development. For example, an infant depends on maternal care during the first weeks of life. However, in developed countries, child abuse, neglect, and lack of quality and time of parenting care have been linked to increased risk of negative long-term consequences on child health (Kaplan, 2001; Mueller et al., 2010; Nelson, 2007). In 2012, the U.S. Department of Health and Human Services referred 3.4 million cases to Child Protective Services, of which most related to child abuse or neglect. Early-life stress (ELS), in the form of childhood maltreatment, is the most common and potentially preventable cause of abnormal brain development (Kaffman and Meaney, 2007). ELS has been associated with social, emotional, cognitive impairment, and psychiatric disorders later in life (Delpech et al., 2016; Hanson et al., 2015; Pechtel and Pizzagalli, 2011). Studies in the early 1950s showed that glucocorticoid levels were higher in premature infants (Levine et al., 1951), potentially because of the neonatal intensive care period (Smith et al., 2011). Stress-related glucocorticoids—cortisol in primates and corticosterone in rodents—have been associated with a reduction in synapse number and altered neuronal assemblies and wiring (Popoli et al., 2011), and they are known to affect neurocognitive development (Carson et al., 2016). Thus, these neuroendocrine factors might affect neurodevelopment early in life. However, how ELS alters brain development associated with multiple clinical outcomes is not yet well understood in humans.

Chronic inflammatory conditions induce age-associated development of an AD-like neuropathology in mice, including increased amyloid precursor protein (APP) loads (Krstic

et al., 2012). Thus, there is an emerging need to understand whether ELS affects the risk of developing AD by activating the brain's innate immunity (Hoeijmakers et al., 2018). ELS aggravates neuropathology and alters disease progression in an AD mouse model (Hoeijmakers et al., 2017). However, the mechanism of microglial contribution to the effects of ELS is still unknown. It is possible that ELS drives neuroinflammation, which will alter microglial activity. ELS increases peripheral inflammation, which might play a role in many psychiatric disorders and alters microglial morphology and density, mainly in the rodent frontal cortex and hippocampus (Baldy et al., 2018; Gómez-González and Escobar, 2010; Roque et al., 2016). ELS is also associated with increased pro-inflammatory cytokines in the brain (Banqueri et al., 2019; Delpech et al., 2016; Gracia-Rubio et al., 2016). Thus, the link between early-life immune activation and deleterious consequences on the brain might affect microglial functions during development. Microglia mature during the second postnatal week (Butovsky et al., 2014; Matcovitch-Natan et al., 2016). The perinatal microglial phenotype resembles the MGnD and DAM phenotypes observed in neurodegenerative diseases (Hagemeyer et al., 2017; Krasemann et al., 2017; Wlodarczyk et al., 2017) and is represented by an APOE expression peak around postnatal day (P) 3, displaying gene characteristics of APOE-dependent MGnD signature (Butovsky et al., 2014; Hagemeyer et al., 2017; Matcovitch-Natan et al., 2016; Wlodarczyk et al., 2017) in a structure-dependent manner. This phenotype is associated with induction of MGnD genes such as *Gpnmb*, *Spp1*, and *Apoe* and an absence of expression of microglial homeostatic genes such as *P2ry12*, *Tgfbr2*, *Mafb*, *Mef2a*, and *Sall1*. However, this phenotype is considered non-toxic during development (Hagemeyer et al., 2017; Wlodarczyk et al., 2017).

Chronic stress might have a direct influence on microglial immune genes such as *APOE* and *TREM2* associated with LOAD in genome-wide association study (GWAS) (Karch and Goate, 2015). These genes are associated with AD cognitive deficits and might be involved in stress-induced neuroinflammation. Human APOE has three alleles: *ε2*, *ε3*, and *ε4*. The *APOE ε4* allele is found in about 15% of the population and in about 60% of patients with AD dementia (Mahley and Rall, 2000). Each additional copy of the ε4 allele is associated with a higher risk of developing AD and an earlier age of dementia onset (Corder et al., 1993; Strittmatter and Roses, 1995). *APOE ε4* allele is the major genetic risk factor for LOAD (Corder et al., 1993; Strittmatter et al., 1993) acting in an age- and gene-dose-dependent manner (Corder et al., 1993; Farrer et al., 1997). APOE ε4 increases Aβ pathology and is associated with impaired memory performance (Liu et al., 2013). However, the pathophysiological mechanisms underlying the genetic association of *APOE ε4* with AD remain elusive. One hypothesis is that long term exposure to chronic stress in older patients, which is associated with increased cortisol levels, might be associated with memory deficits in *APOE ε4* variant carriers (Peavy et al., 2007). Chronic stress was shown to impair cognition in an *APOE4*-humanized mouse model at adult stages (Lin et al., 2016). Although cerebral Aβ deposition might begin 1 to 2 decades before the onset of cognitive impairment (Bateman et al., 2012; Price and Morris, 1999), recent studies suggest functional and structural brain alterations might precede the onset of Aβ deposition in *APOE ε4* carriers (Bookheimer et al., 2000; Shaw et al., 2007). Young adult *APOE ε4* carriers present impaired functional brain activity in regions preferentially affected by AD, decades before their average age at possible dementia onset (Shaw et al., 2007). Moreover, infant *APOE ε4*

carriers have decreased brain volumes in areas affected by AD (Dean et al., 2014). *APOE ε4* adult carriers whom had childhood epilepsy exhibit increased brain Aβ load at late middle age (Joutsa et al., 2017). Thus, pathological conditions associated with activation of APOE signaling, i.e., induced apoptosis during CNS development or activation of glucocorticoids, might lead to an altered developmental APOE-MGnD phenotype, which might lead to later-life cognitive disorders and neurodegenerative diseases such as AD. Genetic variants of *TREM2*, most strongly R47H, also result in an increased risk of developing LOAD and other neurodegenerative diseases (Guerreiro et al., 2013; Ulrich and Holtzman, 2016). AD patients carrying the *TREM2* mutation have increased brain atrophy and cognitive deficits (Jonsson et al., 2013). Moreover, naive *Trem2*$^{-/-}$ mice display impaired microglia-mediated synapse elimination (Filipello et al., 2018). However, how chronic stress affects TREM2 functions in microglia has yet to be investigated. A recent study reported that after chronic stress there is the presence of dark microglia that are TREM2^{+} and associated with AD pathology in APP/PS1 mice (Bisht et al., 2016). However, there is no study investigating cortisol levels or other measure of chronic stress in *TREM2* variant carriers with AD or frontotemporal dementia. With the increase of personalized genetic testing in individuals, a patient's knowledge of their genotype and potential risk of developing AD should be taken into consideration when cognition is measured in the elderly. Living with the knowledge of carrying the *APOE ε4* variant and therefore being at increased risk for developing AD might adversely change the patient's perception of their memory abilities and, thus, their performance on cognitive tests (Lineweaver et al., 2014). More importantly, it can be a source of chronic mental and emotional stress that could enhance the risk of developing neurodegeneration and AD pathology. An interesting observation is that women who breastfed had a lower AD incidence than women who did not (Fox et al., 2013). Ovarian hormone deprivation and/or insulin sensitivity present during breastfeeding might be responsible for this risk reduction. Promoting formula feeding and reducing maternity leave time in developed countries could be directly linked to an increase of AD in women.

Potential treatments for anxiety reduction such as selective serotonin reuptake inhibitors (SSRIs) might be used as preventive measures and treatments for AD (Figure 1). In clinical studies, long-term treatment with SSRIs is associated with reduced rates of dementia and delayed AD progression (Bartels et al., 2018; Kessing et al., 2009). Recently, a study showed that treating APP-PS1 mice with the SSRI fluoxetine improved memory performance, prevented loss of synapses and reduced Aβ plaques levels in the hippocampus (Zhou et al., 2019). Interestingly, these beneficial outcomes are potentially mediated through different cellular and molecular pathways including increased neurogenesis and gliogenesis (Banasr and Duman, 2007; Banasr et al., 2007), but also via activation of the TGF-β pathway in microglia mediated by astrocytic secretion (Caraci et al., 2018). However, genetic risk variants such as *APOE4* and *TREM2 R47H*, which play a role in microglia modulation in AD, should be taken into consideration in future studies.

Diet Habits and Microglia Regulation: Influence of Microbiota

The gut microbiome has attracted significant attention from neuroscientists, because it modulates the CNS in both health and neurodegeneration. The adult microbiota depends on

both genetics (Spor et al., 2011) and environmental factors including diet, maternal environment, and exposure to new microbiota (Sommer and Bäckhed, 2013).

Nutritional habits might influence neurodegenerative disease onset and progression by acting through microglia via peripheral inflammatory pathways such as microbiota. Nutrients and metabolites are known to modulate the immune system (Calder et al., 2017). However, the mechanisms of diet-induced effects are unclear. For example, peripheral inflammation and gut microbiota dysbiosis can tune neuroinflammation and increase the incidence of neurodegeneration (Heneka et al., 2015; Kowalski and Mulak, 2019; Pistollato et al., 2018) but the mechanisms are not well studied. Moreover, many studies have been conducted based on one nutrient at a time. However, the effects of food and nutrients might need to be studied in combination, because they are consumed together (Féart et al., 2009). A lot of attention has focused on the Mediterranean diet, especially in regard to cardiovascular diseases. However, the Mediterranean diet has also been positively associated with a slower rate of cognitive decline (van de Rest et al., 2015) and reduced risk of developing AD (Lourida et al., 2013) (Figure 1). The traditional dietary pattern in Mediterranean countries is characterized by high intake of fruits, vegetables, and wholegrains; moderate intake of fish, poultry, and alcohol (particularly red wine) and low intake of red and processed meats with olive oil used as the main fat source (Davis et al., 2015). On the opposite end of the spectrum, consumption of a Westernized diet, which is more prevalent in Western developed countries, has been associated with an increased risk of developing chronic inflammatory diseases (Uranga et al., 2016). The Western diet is characterized by a high content of proteins (derived from processed meats), saturated fats, refined grains, increased sugar and salt, alcohol, and mostly corn-derived fructose syrup and a decrease in fruit and vegetable consumption (Mozaffarian et al., 2011; Tilg and Moschen, 2015). This diet directly contributes to the development of obesity, metabolic syndrome, and cardiovascular diseases (Shoelson et al., 2007; Tilg and Moschen, 2015). In addition, dietary composition of Western-like diets increases the release of cortisol, influencing the response to stress (Maurer et al., 2003). Western diet has been shown to have an effect on intestinal microbiota, leading to a decrease in total bacteria, as well as specific species such as *Bifidobacterium* and *Eubacterium* (Drasar et al., 1973; Reddy et al., 1975; Wu et al., 2011). On the opposing end, the Mediterranean diet leads to increased levels of microbiota metabolites (short-chain fatty acids [SCFAs]), *Prevotella* bacteria, and other Firmicutes (De Filippis et al., 2016). Beneficial aspects of the Mediterranean diet are potentially because of increases in *Lactobacillus*, *Bifidobacterium*, and *Prevotella* and decreases in *Clostridium* (Bialonska et al., 2010; Clemente-Postigo et al., 2012; Fava et al., 2013; Furet et al., 2010; Koloverou et al., 2016; Queipo-Ortuño et al., 2012), although the specific effects of these alterations on microglia are unknown. Several studies show that obesity, which is associated with the Western diet, and chronic low-grade peripheral inflammation are a risk factor for AD at midlife (Anstey et al., 2011; Chuang et al., 2016; Kivipelto et al., 2005) (Figure 1). Obesity might induce inflammation through alterations of metabolic hormones levels such as insulin (Procaccini et al., 2016). Changes in insulin signaling might affect cognitive deficits and dementia onset as it impairs the control of neuronal excitability for example. Lower serum levels of insulin-like growth factor 1 (IGF-1) have been observed in obese patients (Galli et al., 2012) and might contribute to neuronal loss, as observed in *Igf-1-*

deficient mice (Beck et al., 1995). Consumption of a Western diet also induces astrocytosis and TREM2^{+} microglial activation during aging and in AD mouse model (Cope et al., 2018; Graham et al., 2016). In addition, obesity accelerates AD pathology in *APOE4*-humanized 53FAD mice associated with an increase in Aβ pathology and microglial activation (Moser and Pike, 2017). Thus, obesity associated with a Western diet induces chronic neuroinflammation that might exacerbate AD pathogenesis.

Microglia from adult germ-free (GF) mice, which are not exposed to bacteria throughout life, display altered cell proportions and an immature phenotype, characterized by longer processes and greater numbers of branching and terminal points. This phenotype was associated with impaired CNS immune responses toward immune challenges (Figure 2) (Brown et al., 2019; Erny et al., 2015). Recolonization with complex microbiota or administration of bacterial metabolites, a mix of SCFAs, was able to restore defects in microglia density, proportions, and surface marker expression (Erny et al., 2015). A model of limited microbial diversity was used to examine the impact of a non-diverse gut microbiome (Erny et al., 2015). These mice displayed similarly altered microglia relative to GF mice, suggesting that a non-diverse microbiome is insufficient for normal microglial development. However, recolonization of these mice with a more diverse microbiome allowed microglial maturation to a phenotype similar to adult specific pathogen-free animals. Thus, it might be that the presence of particular microbiota species or a sufficiently diverse microbiome is required for proper microglial function. In humans, an individual's microbiota is relatively stable with day-to-day variation (Costello et al., 2009). Large disruptions occur after antibiotic administration, infection, and large diet changes (David et al., 2014). Depending on the disruption frequency and length, microbiota recovery might be impaired (Dethlefsen et al., 2008; Levy et al., 2017; Ubeda and Pamer, 2012). The use of antibiotics might affect microglial function, which must be taken into account when considering the large-scale use of antibiotics. Interventions to enrich or entire reconstruction of an individual's microbiome by probiotics or fecal matter transplant (FMT) might become viable options.

The maternal gut microbiome is also important for microglial development and maturation. The maternal gut microbiome helps shape microglial development close to birth. At embryonic day (E) 14.5, embryonic microglia from offspring of GF dams display only minor differences compared with controls; however, microglia isolated closer to birth, at E18.5, displayed considerable differences in transcriptomes, morphology, and distribution. Importantly, a strong gender effect was observed; major differences were specifically observed in embryonic males, whereas females displayed the largest differences later in adulthood (Thion et al., 2018). Metabolites such as SCFAs have been shown to influence microglial maturation and phenotype in health and disease (Hara et al., 1999; Raybould, 2010). Mice lacking free fatty acid receptor 2 (FFAR2), a G protein-coupled receptor required for SCFA signaling in the gut, exhibited a similar microglial phenotype to that observed in GF mice (Erny et al., 2015), although the mechanism of action is still unclear (Chen et al., 2007; Erny et al., 2015). These important observations open up interesting avenues to explore the role of microbiome modulation of microglia in development and its potential consequences on neurodegeneration in adulthood (Figure 2). In humans, maternal anxiety during pregnancy (Hechler et al., 2019) and ELS (Jacquot et al., 2011; Rougé et al.,

2010) can affect microbial composition in infants, linking psychological symptoms in pregnancy to microbiota alterations in offspring. The use of probiotics may ameliorate these effects (Cowan et al., 2019).

Several bidirectional signaling pathways have been identified by which the gut microbiota affects microglia, including immune and neural pathways (Figure 2) (Bravo et al., 2011; Erny et al., 2015; Tan et al., 2014b). Efferent signals can modulate gastroin-testinal (GI) motility, secretions, and permeability, modifying the microbiome environment and its composition (Collins et al., 2012). The vagus nerve connects the gut and the brainstem, serving as the afferent conduit for communicating satiety, stress, and mood, and recognizes gut microbial products (Forsythe et al., 2014; Goehler et al., 2005). The inflammatory state of the gut can directly activate chemoreceptors located at vagal nerve endings to influence microglia and the level of inflammation in the CNS (Forsythe et al., 2014). A peripheral immune challenge can cause upregulation of anti-inflammatory pathways in the brain via the vagus nerve, including decreased microglial pro-inflammatory cytokines (Frasch et al., 2016; Kaczmarczyk et al., 2017; Meneses et al., 2016). Microbiota can influence the CNS through direct modulation of the peripheral immune system or by regulating intestinal permeability to control the entry of pathogenic, immune-stimulating, and neuroactive substances (Karczewski et al., 2010; Kelly et al., 2015). Astrocytes might also control microglia regulation during aging and in disease. Indeed, it has been shown that in combination with microbiota changes, dietary tryptophan is metabolized by the gut into aryl hydrocarbon receptor (AHR) agonists that have an effect on astrocytes to limit neuroinflammation via interferon type I (IFN-I) signaling (Rothhammer et al., 2016). In addition, microbial metabolites might limit pathogenic activities of microglia and astrocytes and suppress CNS inflammation via transforming growth factor α (TGF-α) and vascular endothelial growth factor B (VEGF-B) produced by microglia (Rothhammer et al., 2018). Mice fed a high-fat diet show elevated levels of Firmicutes and Proteobacteria compared with Bacteroidetes, a finding replicated in obese patients. *Akkermansia muciniphila* is one identified Bacteroidetes that is less abundant in obese individuals and has been implicated in intestinal integrity (Dao et al., 2016). A pro-inflammatory response could compromise the integrity of the blood-brain barrier (BBB) (Rochfort et al., 2014), and increased circulation of BBB-permeable cytokines and neurotoxic compounds could directly lead to microglial activation (Qin et al., 2008; Riazi et al., 2008). Microbiome-microglia communication might rely on specific microbiota and is likely mediated via multiple mechanisms. Identification of individual metabolites and their effects on microglia is a critical step in developing any therapeutic strategy. The effects of the microbiome on microglial phenotype and functions, such as phagocytosis of various substrates, milieu sensing, tolerance, and migration, remain to be investigated. Interesting questions remaining to be explored are whether and how microglia might modulate the composition or function of the microbiome.

Microbiome-Microglia Modulation in Neurodegeneration

Preclinical and human cross-sectional studies have associated microbiome alterations with several neurodegenerative diseases, including Parkinson’s disease (PD) (Fasano et al., 2013; Keshavarzian et al., 2015; Tan et al., 2014a), AD (Harach et al., 2017; Ho et al., 2018; Minter et al., 2016), amyotrophic lateral sclerosis (ALS) (Rowin et al., 2017; Zhang et al.,

2017b), and multiple sclerosis (MS) (Cekanaviciute et al., 2017; Kosmidou et al., 2017; Miyake et al., 2015).

PD is the second most common neurodegenerative disorder after AD and is characterized by dopaminergic neuron death in the substantia nigra and neuronal accumulation of α-synuclein (Goedert et al., 2013). Alterations of the microglial microenvironment might trigger a pathogenic phenotype associated with release of pro-inflammatory cytokines and other neurotoxic compounds (Zhang et al., 2005). Large-scale microglial molecular profiling in animal models of PD has not yet been conducted, but activated microglia are known to be prominent in both mouse models and human PD (Joers et al., 2017), including expression of AXL associated with MGnD/DAM microglia (Keren-Shaul et al., 2017; Krasemann et al., 2017). One hypothesis contends that sporadic PD begins in the gut by α-synuclein aggregation, spreading via the vagus nerve (Braak et al., 2004; Rietdijk et al., 2017). Indeed, vagotomy might be associated with reduced risk of PD development in humans (Svensson et al., 2015a). In support of this hypothesis, a recent study found that gut injection of α-synuclein fibrils converts endogenous α-synuclein into a pathological species that spreads to the brain, leading to PD features. Consistently, vagotomy or α-synuclein deficiency prevented neuropathological and neurobehavioral deficits (Kim et al., 2019). Gut-associated symptoms, including chronic constipation and GI distress, precede motor symptoms in up to 80% of PD patients (O'Sullivan et al., 2008). Thus, it would be important to investigate whether patients with GI distress exhibit increased levels of α-synuclein production in the gut, thereby linking the GI issues with the potential mechanism of spreading to the brain. Moreover, PD patients exhibit significantly altered gut microbiome (Hill-Burns et al., 2017) and reduced SCFA concentrations (Unger et al., 2016). GF mice that overexpress human α-synuclein display reduced motor deficits, GI dysfunction, and microglial activation (Figure 2) (Sampson et al., 2016). Furthermore, administering SCFAs to these GF transgenic mice increased microglial activation and induced motor deficits (Sampson et al., 2016). Interestingly, in a toxin-induced model of PD, FMT attenuated microglial activation, along with motor deficits and decreased SCFAs (Sun et al., 2018). This supports the idea that microbiome components might have a beneficial effect and, if identified, could be therapeutic targets. Microglial phenotype in PD still needs to be defined to put their role into context with other neurodegenerative diseases.

The gut microbiome might be an important factor in the etiology of AD. Microbial metabolites were measured in the CSF of AD patients and associated with AD biomarkers, including phosphorylated tau and Aβ (Vogt et al., 2018). In addition, aged individuals exhibit a different microbiome (Claesson et al., 2011), which supports the possibility that an altered microbiome mediated by aging is associated with the AD etiology and pathogenesis. When comparing fecal microbiomes and SCFAs between AD and wild-type (WT) mice at different ages, the proportions of certain microbiota were different, including elevations in Verrucomicrobia and Proteobacteria, whereas the levels of SCFAs were reduced (Zhang et al., 2017a). An interesting approach would be to investigate whether FMT from old to young AD mice would exacerbate disease progression, as well as whether young-to-old microbiome transfers may be a treatment for AD. The oral microbiome has also become of interest after the pathogen *Porphyromonas gingivalis*, involved in chronic periodontitis, was identified in the brain of AD patients, and oral infection in mice resulted in brain

colonization and increased Aβ production (Dominy et al., 2019). GF AD mice displayed a reduction in Aβ pathology, and colonization of these mice increased pathology (Harach et al., 2017). Furthermore, long-term antibiotic treatment in an AD mouse model decreased Aβ plaque deposition associated with altered cytokine and chemokine signatures and microglial morphology (Figure 2; Minter et al., 2016). Strikingly, short-term postnatal antibiotic treatment (P14–P21) resulted in lasting gut microbiome alterations associated with a reduction in Aβ deposition later in life, along with alterations in the CNS inflammatory milieu and reduced plaque-associated microglia (Minter et al., 2017). Aβ pathology amelioration by antibiotics occurs only in brains of male mice associated with restoration of M0-homeostatic microglia. In addition, FMT of microbiota from age-matched AD male mice into antibiotic-treated AD males restored the gut microbiome and partially restored Aβ pathology and microglial morphology (Dodiya et al., 2019). In contrast to depleting the microbiome, administration of *Lactobacillus plantarum* was able to ameliorate cognitive deficits in AD mice (Nimgampalle and Kuna, 2017).

ALS is a fatal neurodegenerative disease characterized by the progressive loss of motor neurons. Most ALS patients die within three to five years of diagnosis because of respiratory paralysis (Alonso et al., 2009). Microglia isolated from the SOD1 mouse model of ALS upregulate MGnD/DAM pathways similar to microglia from AD mice, including APOE expression (Butovsky et al., 2015; Chiu et al., 2013; Krasemann et al., 2017), a finding confirmed in human ALS (Butovsky et al., 2015). The M0-homeostatic microglial signature is lost as early as 2 months before disease onset in SOD1 mice (Butovsky et al., 2015). Similar to AD, ALS is an age-dependent disease, potentially implicating age-related changes in the microbiome to disease vulnerability. SOD1 mice had an altered microbiome profile with reduced levels of *Butyrivibrio fibrisolvens*, *Escherichia coli*, and *Fermicus*, which was detected before disease onset (Wu et al., 2015), potentially linking changes in the gut microbiome to microglial changes. Importantly, *Butyrivibrio fibrisolvens* is a butyrate-producing bacterium, and feeding SOD1 mice with the SCFA restored microbial homeostasis, improved gut integrity, and prolonged lifespan (Zhang et al., 2017b). In a small pilot study, the gut microbiome of 5 human ALS patients was examined, and all displayed altered gut microbiome characterized by low diversity with relatively intact abundance (Rowin et al., 2017). A recent study found that GF or antibiotic-treated SOD1 mice had significantly exacerbated disease (Figure 2; Blacher et al., 2019). This work identified 11 distinct microbiota that correlated with disease severity and showed through individual supplementation that *Akkermensia muciniphila* ameliorated disease and *Ruminococcus torques* and *Parabacteroides distasonis* exacerbated disease. Interestingly, the authors identified that *Akkermensia muciniphila*-treated SOD1 mice displayed an accumulation of nicotinamide (NAM) in the CNS. They went on to systemically administer NAM, which significantly improved the performance of SOD1 mice in both behavioral and neurological motor tests and produced a trend toward increased survival. The authors compared the microbiome composition of ALS patients with healthy control household members and found significant differences overall, but only five specific bacterial species reached near significance. Functionally, the ALS microbiomes showed differences in bacterial gene content, with decreases in several key genes involved in NAM metabolism (Blacher et al., 2019). These findings that microbiome depletion worsens disease in SOD1 mice stand in

contrast to those in other neurodegenerative models. However, they are consistent with the opposing effects of minocycline in MS and ALS (Gordon et al., 2007; Metz and Eliasziw, 2017). Although the diseases share a common symptom, neurodegeneration, these discordant effects of microbiome depletion emphasize the consideration that opposing, disease-specific treatment approaches might be necessary. It is also possible that microglia might not be involved in disease pathogenesis in all neurodegenerative diseases. Nonetheless, defining microglia in the context of microbiome-depleted ALS models will likely be an area of intense research to investigate how their function in disease might differ in these models and to discover mechanisms that could serve as therapeutic targets.

MS is a chronic, inflammatory disease characterized by immune-mediated CNS demyelination resulting in neurological disorders. Microglia play an important role in MS, including during neurodegeneration in later stages. In the experimental autoimmune encephalomyelitis (EAE) mouse model of MS, microglia have different transcriptional phenotypes associated with disease stages. At disease peak, their phenotype is similar to that observed in other neurodegenerative disease models, such as AD and ALS (Chiu et al., 2013; Krasemann et al., 2017). In human MS, microglia also have multiple phenotypes dependent on disease stage (relapsing/remitting or progressive) and lesion type (active or chronic) (Zrzavy et al., 2017). Microglia lose the expression of homeostatic markers, including P2RY12, and express pro-inflammatory markers, including phagocytic, antigen presentation, and reactive oxygen species markers (Zrzavy et al., 2017). Minocycline, which has been shown to specifically affect microglia (Kobayashi et al., 2013; Sriram et al., 2006), showed positive trends in a trial in MS (Metz and Eliasziw, 2017), although it worsened disease in ALS patients (Gordon et al., 2007). However, it is possible that minocycline affected the microbiota, which then affected disease progression (Vaughn et al., 2017). EAE studies showed that oral administration of antibiotics significantly reduced disease severity (Ochoa-Repáraz et al., 2009) and GF mice display attenuated EAE development (Lee et al., 2011; Figure 2). In a clinical study, elevated levels of specific microbiota (*Akkermansia muciniphila* and *Acinetobacter calcoaceticus*) were observed in MS patients (Jangi et al., 2016). Transplantation of these bacteria from patients with MS into GF mice leads to EAE exacerbation (Cekanaviciute et al., 2017). Further studies have shown that microbiota from pediatric MS patients exhibit relatively greater pro-inflammatory trends and that depletion of certain flora might be linked to increased relapse risk (Tremlett et al., 2016; Tremlett and Waubant, 2018). Treatment of MS with the probiotic VSL3, a cocktail of eight bacteria with a good safety profile, enriched specific microbiota in the intestines and inhibited monocyte-mediated peripheral inflammation, an effect that disappeared after discontinuation (Tankou et al., 2018). Although the microglial phenotype in EAE and MS has been defined and significant investigation into the role of microbiota is ongoing, defining work into how microglia and the microbiome interact in MS and EAE remains to be conducted. One important question to be addressed is how microbiome alterations at different stages of the disease course might modulate disease progression and microglial phenotype.

A significantly altered gut microbiome is a common feature in neurodegenerative disease. Altered microbiomes might have many effects on brain physiology, including the consistent observation of an immature and functionally impaired phenotype in microglia. It is also possible that in microbiome-depletion conditions, microglia might be reset to a homeostatic

state. This hypothesis is supported by the appearance of M0-homeostatic microglia in the antibiotic-treated AD model (Dodiya et al., 2019). The identification of specific microbiota associated with worsening or ameliorated pathology is a critical step to investigate precise underlying mechanisms. Putative molecules are being identified that can potentially move to clinical trials to investigate their function in humans. Further work is needed to explore microbiome-mediated maintenance and polarization of M0 and MGnD and DAM microglia and to further define specific microbiome-dependent microglial phenotypes and functions in neurodegeneration. It is clear that lifestyle, including dietary choices and treatments like antibiotics, can significantly affect the human microbiome and microglia, possibly affecting predisposition to neurodegeneration.

Circadian Rhythm and Sleep Patterns Influence on Microglia Regulation in Neurodegeneration

We spend one-third of our lives sleeping. Sleep is required to maintain normal neurocognitive and immune functions (Dumaine and Ashley, 2015). During sleep, the brain processes information, consolidates newly formed memories (Abel et al., 2013), promotes spatial learning (Nguyen et al., 2013b), and clears the brain (Xie et al., 2013). Sleep loss might result from sleep deprivation (SD), chronic sleep restriction, and sleep fragmentation. Sleep fragmentation is commonly seen in sleep disorders such as obstructive sleep apnea or restless legs syndrome (Reynolds and Banks, 2010). SD and chronic sleep restriction are mainly caused by work, lifestyle, drugs, and aging.

Sleep plays an important role in Aβ clearance (Xie et al., 2013). The sleep-wake cycle can regulate interstitial fluid (ISF) and CSF levels of Aβ (Figure 3). It has been shown that Aβ clearance pre-dominantly occurs during sleep (Kang et al., 2009), which was ascribed to the glymphatic pathway operating most efficiently during sleep (Iliff et al., 2012; Lee et al., 2015; Louveau et al., 2015; Xie et al., 2013). Using real-time *in vivo* two-photon microscopy, it has also been shown that patrolling monocytes might crawl onto the luminal walls of blood vessels to clear and carry Aβ out of the brain (Michaud et al., 2013). Interestingly, neuroimaging studies showed that short sleeping duration and poor sleep quality in cognitively healthy middle-aged and aged people might be associated with higher Aβ accumulation (Brown et al., 2016; Spira et al., 2013; Sprecher et al., 2015). A human positron emission tomography (PET) study showed that just one night of SD significantly induced Aβ levels in the brain (Shokri-Kojori et al., 2018). Acute SD is enough to elevate Aβ levels in mouse ISF (Kang et al., 2009) and human CSF (Ooms et al., 2014). Chronic sleep restriction significantly increases the ISF level of Aβ in *Drosophila* (Tabuchi et al., 2015) and mouse (Kang et al., 2009) models of AD. Sleep disturbance and circadian rest-activity pattern alterations observed in preclinical AD studies might be risk factors for developing AD (Jagust, 2016; Mucke and Selkoe, 2012; Musiek et al., 2018). Furthermore, in human brains, the rhythmic DNA methylation of brain and muscular Arnt-like 1 (*BMAL1*) is altered in AD, which might be one reason for the circadian alterations in AD brains (Cronin et al., 2017). In addition to Ab, CSF tau and α-synuclein might increase in sleep-deprived humans. In a transgenic P301S tau mouse model and in human CSF, tau

levels were increased after chronic SD that could facilitate the spread of tau pathology (Holth et al., 2019) (Figure 3).

SD and sleep restriction alter brain functions at molecular, cellular, and network levels, which might lead to severe cognitive and emotional problems (Musiek and Holtzman, 2016; Pires et al., 2016). SD-induced cognitive impairment is associated with elevated inflammatory cytokine levels in the hippocampus, gliosis, and morphological changes of microglia and astrocytes (Wadhwa et al., 2017a). Several studies have shown that SD modulates astrocytes and microglial phenotypes and functions, which might contribute to neurodegeneration (Figure 3). Interestingly, inhibiting microglial activation with minocycline during SD decreases the hippocampal immunoreactivity and improves cognition and adult hippocampal neurogenesis (Wadhwa et al., 2017b). Tyrosine kinase receptor Mertk and its ligand GAS6, which mediate microglial process extension and induce phagocytosis (Fernandes et al., 2016; van der Meer et al., 2014), are upregulated in both microglia and astrocytes during SD (Grommes et al., 2008). Both acute SD and chronic SD impair the cognition and immune functions, in which microglia play an active role. Further studies on microglial molecular signature alteration during SD are needed. The sleep-wake cycle affects synaptic remodeling via microglia. Mice lacking cathepsin S, which is a microglial-specific lysosomal cysteine protease, present impaired diurnal variations in spine density and activity of cortical neurons (Hayashi et al., 2013). Phagocytic microglia mediate synapse elimination via C1q and C3 complement factors (Schafer et al., 2012; Stevens et al., 2007). In addition, early synaptic loss in AD mouse models is mediated by microglia through C1q and C3 (Hong et al., 2016) (Figure 3). Interestingly, C3 levels are upregulated in the brain after acute and chronic SD (Bellesi et al., 2017). Thus, complement-mediated synaptic pruning might be exacerbated by SD, which might contribute to early synaptic loss and AD onset. Potential molecular pathways and upstream regulators could be therapeutic targets for preventing brain impairments caused by sleep loss.

Microglial inflammatory responses can be tightly controlled by the circadian clock and, if altered, might predispose individuals to neurodegeneration. When immune challenged, microglia display higher expression of pro-inflammatory cytokines, and their process extension is significantly increased during the light phase (Fonken et al., 2015; Takayama et al., 2016). In addition, chronic stress during the light phase could amplify microglial responses (Fonken et al., 2016b). Glucocorticoids play a pivotal role in stress-induced priming of neuroinflammatory responses (Frank et al., 2012, 2014). Thus, the circadian dependency of microglia responsiveness to glucocorticoids might be one mechanism for the diurnal rhythm of microglia toward inflammatory stimuli (Fonken et al., 2016b). Another possibility could be that circadian genes are involved in regulating immunological activities of microglia. For example, circadian protein circadian locomotor output cycles kaput (CLOCK) regulates NF-κB-mediated transcription (Spengler et al., 2012). Circadian gene BMAL1 has been found to regulate diurnal oscillation of $Ly6C^{Hi}$ classical inflammatory monocytes in trafficking to sites of inflammation (Nguyen et al., 2013a). $BMAL1^{-/-}$ mice have been shown to present massive gliosis and degeneration of synaptic terminals (Musiek et al., 2013). miR-155 plays an important role in induction of inflammatory microglial phenotype in neurodegeneration (Butovsky et al., 2012, 2015; Koval et al., 2013). BMAL1 inhibits NF-kB activation and suppresses miR-155 in peripheral myeloid cells (Curtis et al.,

2015). In addition, depletion of miR-155 diminishes the circadian rhythm of cytokine responses to lipopolysaccharide (LPS) (Curtis et al., 2015). Thus, circadian genes regulate the immune response of microglia and might contribute to neurodegeneration directly by enhancing neuroinflammation or via alterations of the microbiome. A jetlag circadian paradigm can change gut microbiota (Phan and Malkani, 2018) and thus potentially microglial responses. Future studies are needed to investigate the association between circadian rhythm disorder and microglial functional alterations, as well as their contribution to neurodegeneration.

Aging is associated with altered sleep patterns and disrupted circadian rhythm of microglia. Sleep in aged people is characterized by an increased number of arousals from sleep, decreases in total sleep time and sleep efficiency, and a reduction of nonrapid eye movement (non-REM) sleep (Miner and Kryger, 2017). In addition, the common feature of age-related change in circadian rhythmicity is the shift of sleep to earlier hours, i.e., early morning awakening hours, that are often earlier than desired (Duffy et al., 2015). Microglia isolated from aged animals displayed suppressed expression of diurnal clock genes and inflammatory cytokines compared with young microglia (Fonken et al., 2016a). Glucocorticoid rhythm is dysregulated in aged hippocampus (Herbert et al., 2006), despite aged microglia maintaining the responsiveness to corticosterone (Fonken et al., 2016a). The dysregulated glucocorticoid rhythm in aging subjects is associated with chronic stress, which contributes to neurodegeneration (Vyas et al., 2016). Aging-related microglia-specific circadian genes expression profiling is still lacking. In the future, targeted therapies that enhance molecular rhythmicity might be a potential approach to prevent age-related sleep-wake change and improve cognition. Deeper understanding of how the circadian clock change during aging influences microglial function might create insight to regulate circadian clock and improve health and longevity.

Exercise Modulates Microglia in Neurodegeneration

The neuroprotective roles of physical exercise and environmental enrichment have been recognized in several studies (Chen et al., 2016; Ziv et al., 2006). Beneficial effects of physical exercise include anti-inflammatory effects, improvement of hippocampal neurogenesis, and stimulation of brain-derived neurotrophic factor (BDNF) release (Gleeson et al., 2011). In addition, physical exercises reduce anxiety and modulate the gut microbiota, independent of diet, and have positive health effects in the brain (Mailing et al., 2019) (Figure 3). An hour of wheel running by mice can increase the relative abundance of *Lachnospiraceae*, which is positively associated with reduced anxiety-like behavior in mice (Kang et al., 2014). Accumulating evidence also suggest that aerobic exercise could protect the brain from systemic inflammation by directly regulating inflammatory cytokines (Beavers et al., 2010), by mediating the secretion of anti-inflammatory adipokines and myokines through the muscle-adipose crosstalk (Kelly, 2018; Leal et al., 2018; Mazur-Bialy et al., 2017), or via the hypothalamic-pituitary-adrenal axis (Ortega, 2016). The effects of short- or long-term physical exercises on brain functions have been shown in various AD mouse models and include improvement of cognitive performance, reduction of pro-inflammatory cytokine levels, and most importantly, amelioration of Aβ deposition and tau pathology (Kelly, 2018). Physical exercises reduce the production of cerebral pro-

inflammatory cytokines by promoting clearance of Aβ (Prado Lima et al., 2018) and reduce $GFAP^+$ astrocyte density in the hippocampus of APP-PS1 (Tapia-Rojas et al., 2016). Environmental enrichment has been shown to reduce Aβ levels in an AD mouse model (Lazarov et al., 2005) and to prevent microglia-mediated neuroinflammation in injected with human Aβ oligomers (Xu et al., 2016). Physical exercise and environmental enrichment ameliorate Aβ and tau pathology not only when they are provided before the pathology starts to show but also at the late stage of the disease (Leem et al., 2011; Tapia-Rojas et al., 2016). In a 16-month-old transgenic tau mouse model, treadmill running for 3 months could significantly decrease tau phosphorylation, as well as microglia-induced neuroinflammation (Leem et al., 2011). The anti-inflammatory effects of exercises were also shown in a PD mouse model (Svensson et al., 2015b). Beneficial effects include amelioration of motor deficits and reduction of pro-inflammatory cytokine secretion (Svensson et al., 2015b). Treadmill running for 30 min/day for 2 weeks in rats leads to reduced expression of downstream targets of Toll-like receptor (TLR) pathways, such as myeloid differentiation primary response gene 88 (MyD88) and NF-κB (Altmeppen et al., 2013). The reduction in TLR signaling in microglia could be one mechanism for the anti-inflammatory effects of physical exercise. Exercise could reverse aging and infection-induced memory deficits (Barrientos et al., 2011) by directly increasing the levels of interleukin-10 (IL-10), an anti-inflammatory cytokine in the hippocampus of aged rat (Gomes da Silva et al., 2013). $CD86^+$ and major histocompatibility complex class II-positive (MHC class II^+) microglia are increased with aging (Kohman et al., 2013). Wheel running by mice has been shown to decrease the proportion of both $CD86^+$ and MHC class II^+ microglia in the hippocampus. However, these effects are gender dependent, and aged male mice showed a decrease in $CD86^+$ microglia and an increase in MHC class II^+ microglia (Kohman et al., 2013). Microglial functions might also be restored in an enriched environment promoting neuronal support. In addition, the beneficial effect of exercise on cognition in a transgenic AD mouse model has been suggested to be mediated by both improvement of neurogenesis and elevation of BDNF secretion genetically and pharmacologically (Choi et al., 2018). Interestingly, elevated neurogenesis alone could not restore cognitive impairment in 53FAD mice. The effect has to be combined with increased BDNF. This will be a potential way to improve cognition in neurodegeneration. However, it remains to be determined whether these beneficial effects are microglia mediated. In summary, exercise and enriched environment could play a strong protective role in aging and neurodegeneration by reducing neuroinflammation and modulating microglial phenotypes and functions.

Concluding Remarks

Here we reviewed current knowledge of how modern societal lifestyle factors such as diet, sleep patterns, physical activity, and microbiota affect microglia regulation and neurodegeneration in both animal models and humans. Determining the true role and importance of microglia in the onset and progression of neurodegenerative diseases remains an active area of research, as does how different lifestyle factors regulate microglia to potentially lead to increased susceptibility to neurodegeneration. It is important to consider that neurodegenerative diseases are complex and multi-factorial, and an individual's predisposition to neurodegenerative disease is likely driven by numerous other factors as

well. Recent findings have made clear the importance and impact of the gut microbiome on microglial phenotype and pathology in models of neurodegenerative diseases. However, further work remains to be done on how microglia and the gut microbiome might interact and whether findings will be validated in human studies. Furthermore, precisely how the composition of the human gut microbiome over the lifespan, potentially changing with dietary choices, living environments, and age, contributes to predisposition to neurodegenerative disease remains a necessary question to answer. Such information would allow individuals to make informed choices, as well as allowing potential governmental regulatory oversight over food options. Microglial immune response is controlled by the circadian clock. Circadian rhythm sleep disorders and sleep loss contribute to neurodegeneration via microglia-induced neuroinflammation and elevated protein aggregation. Circadian rhythm also strongly affects stress level and the composition of the gut microbiome, which have been shown to closely relate to neurodegeneration. Physical exercises and environmental enrichment play a neuroprotective role by mediating anti-inflammatory effects, promoting neurogenesis, and regulating the gut microbiota. Mediterranean diet patterns have been observed in different countries but are particularly effective in so-called blue zones. In these areas, including Sardinia, Italy; Okinawa, Japan; Loma Linda, California; Nicoya Peninsula (Costa Rica); and Icaria, Greece, populations share similarities in their diet pattern but also common features regarding lifestyle stress factors such as stress-free environment, regular physical exercise, and familial and social life (Buettner and Skemp, 2016), and a higher rate of longevity (Pes et al., 2013). In Sardinia, they also present lower cognitive deficits, better working memory performance, and lower levels of depressive symptoms associated to their lifestyle pattern (Fastame, 2014; Fastame et al., 2015; Fastame and Penna, 2014). Microbiome composition and sleep patterns should be investigated in these populations to put findings from animal models in a human context. Altogether, better use and control of our diet, environment, and our way of living might lead to decreased susceptibility to neurodegenerative disorders.

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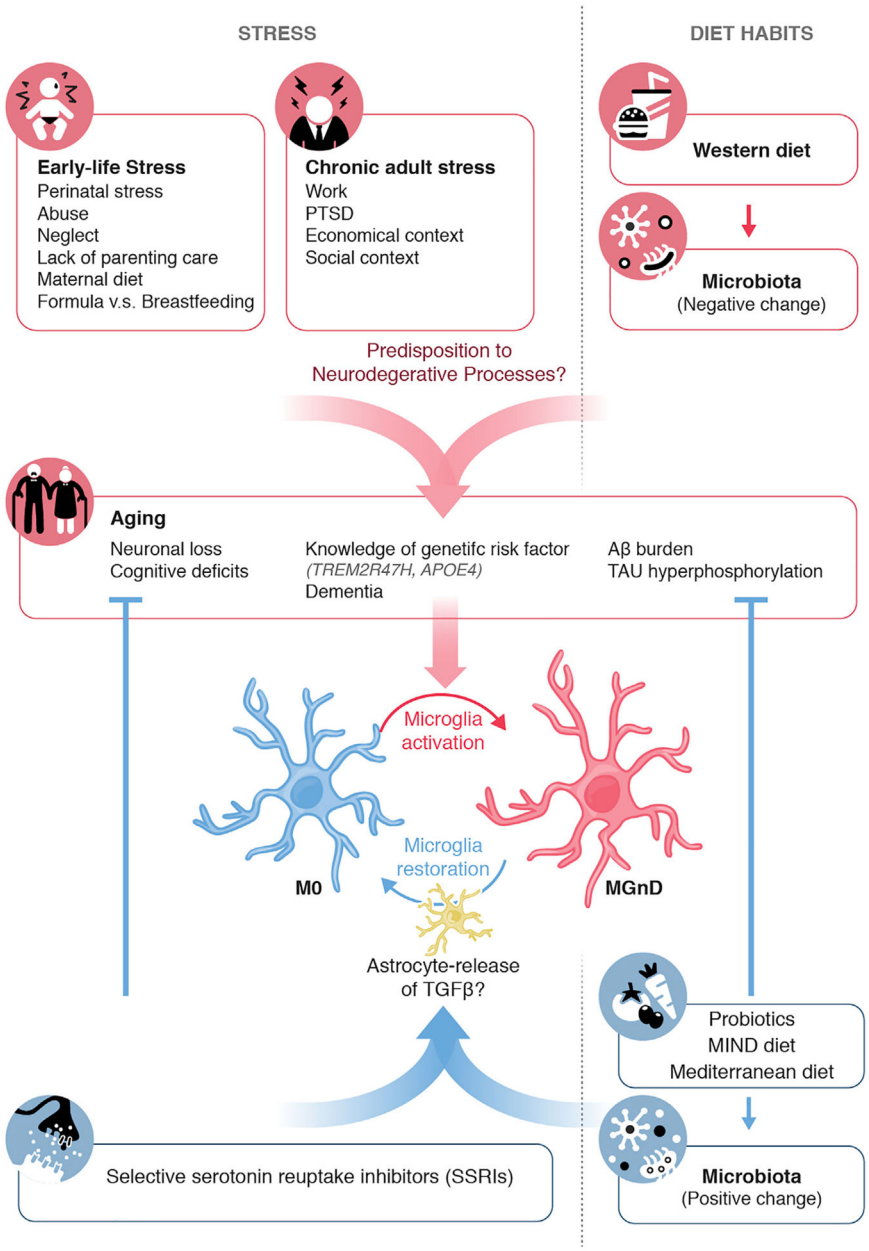

Figure 1. Lifestyle Factors Might Hijack Microglia Regulation and Predispose Individuals to Neurodegeneration

ELS, chronic adult stress, or changes in diet, microbiota, or social contexts might predispose individuals to neurodegenerative disease onset, as observed by associations with neuronal loss, cognitive deficits, and AD-related pathology. These phenotypes during aging could be influenced by a change in an individual's dietary pattern, changes in an individual's microbiota, and drug medications such as SSRIs. This preventive mechanism could be acting through astrocyte release of TGF-b that could modulate microglial functions and restore a phenotype that can stop neurodegeneration.

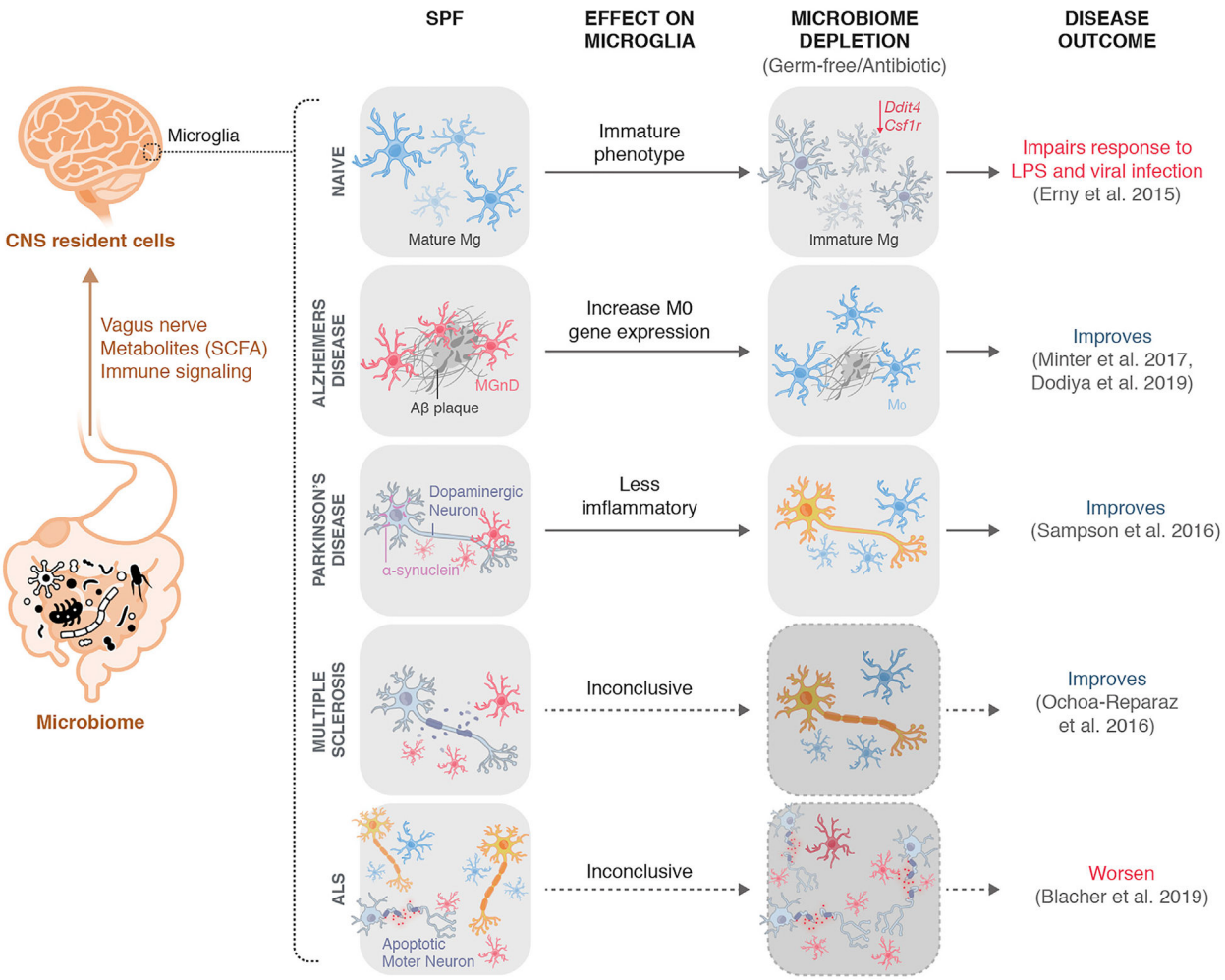

Figure 2. Microbiome Depletion Modulates Microglial Phenotype and Neurodegenerative Disease Pathology

The microbiome can communicate with CNS resident cells, including microglia, through various pathways, including the vagus nerve, microbial metabolites (SCFAs), and direct and in-direct immune signaling pathways. Upon microbiome depletion either in a GF context or after antibiotic administration, microglia adopt an immature phenotype associated with impaired responses to LPS and viral infections. In the context of neurodegeneration, microbiome depletion in AD and PD is associated with amelioration of disease progression and pathology, with increased M0-homeostatic gene expression in microbiome-deplete AD mice and evidence of less inflammatory microglia in microbiome-deplete PD mice. In ALS, disease pathology is markedly worsened in a microbiome-depleted context. Microglial phenotype remains to be explored in microbiome-depleted ALS mice.

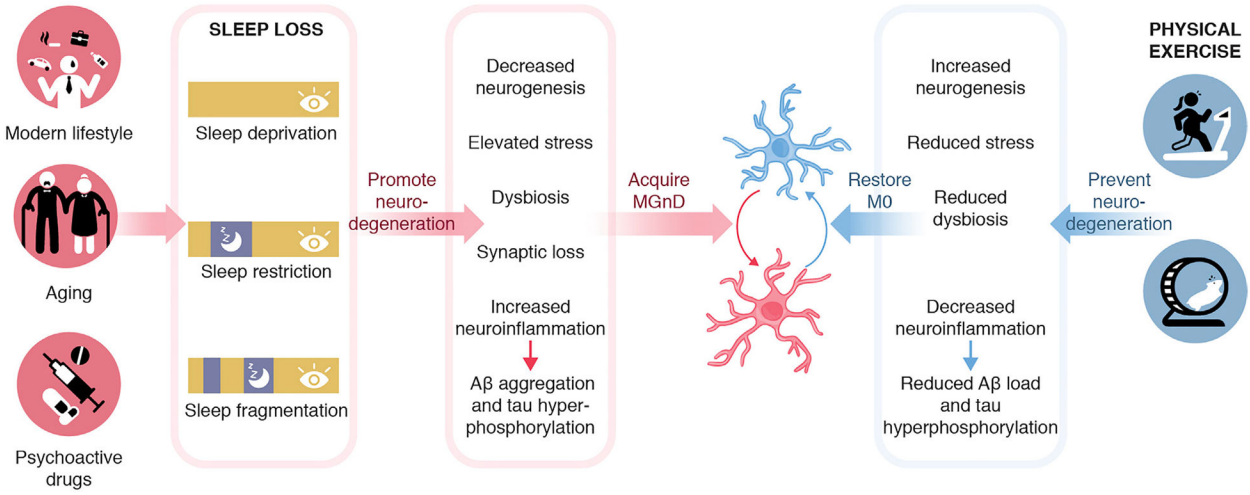

Figure 3. Sleep Loss Might Promote Neurodegenerative Functions of Microglia and Can Be Prevented by Physical Exercise

Forms of sleep loss, including deprivation, restriction, and fragmentation, could promote neurodegeneration by decreased neurogenesis, elevated stress, altered microbiome composition, synaptic loss, increased neuroinflammation, and protein aggregation. These conditions could lead to the acquisition of MGnD, which could exacerbate disease. Conversely, physical exercises might support increased neurogenesis, reduced stress, altered microbiome composition, reduced neuroinflammation, and protein aggregation, which might restore microglial phenotype and prevent neurodegeneration.