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Differential contribution of microglia and monocytes in neurodegenerative diseases

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Abstract

Neuroinflammation is a hallmark of neurodegenerative diseases including Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS). Microglia, the innate immune cells of the CNS, are the first to react to pathological insults. However, multiple studies have also demonstrated an involvement of peripheral monocytes in several neurodegenerative diseases. Due to the different origins of these two cell types, it is important to distinguish their role and function in the development and progression of these diseases. In this review, we will summarize and discuss the current knowledge of the differential contributions of microglia and monocytes in the common neurodegenerative diseases AD, PD, and ALS, as well as multiple sclerosis, which is now regarded as a combination of inflammatory processes and neurodegeneration. Until recently, it has been challenging to differentiate microglia from monocytes, as there were no specific markers. Therefore, the recent identification of specific molecular signatures of both cell types will help to advance our understanding of their differential contribution in neurodegenerative diseases.

Keywords

Microglia; Monocytes; Neurodegeneration; Neuroinflammation

Introduction

Neurodegeneration is a common pathological hallmark of many central nervous system (CNS) diseases and disorders. It results in disturbances of CNS homeostasis and neuronal function ultimately leading to neuronal death. Over the past few decades, research studies have focused on understanding and resolving the underlying mechanisms of neurodegeneration. The most known and studied neurodegenerative diseases include Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS). In addition, this review will also cover multiple sclerosis (MS), which has long been

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considered primarily an autoimmune disease (Lassmann et al. 2012). However, studies have described axonal alterations and lesions in MS plaques that are associated with the clinical neuropathology (Ferguson et al. 1997; Trapp et al. 1998; Lassmann et al. 2012). Thus, it has been acknowledged that MS is a combination of inflammatory processes and neurodegeneration, typically at later stages of the disease (Chaudhuri 2013; Kawachi and Lassmann 2017).

Familial cases of neurodegenerative diseases have been very useful in identifying the genetic mutations that could increase an individual's vulnerability to develop the disease. These include mutations in the superoxide dismutase 1 (SOD1) gene, which have been implicated in the origin of ALS, in the β-amyloid (Aβ) precursor protein in AD, or in α-synuclein for PD (Goate et al. 1991; Rosen et al. 1993; Polymeropoulos et al. 1997). Several genetic variations were also identified through genome-wide association studies (GWAS). However, many sporadic cases occur due to unknown factors. Although the causes of neurodegenerative diseases remain largely unknown, there is a growing amount of evidence showing that inflammatory and immune responses may contribute to disease progression.

Inflammation is a defense mechanism that counters diverse insults by removing or inhibiting pathogens (Wyss-Coray and Mucke 2002). In neurodegenerative diseases, inflammation results mainly from the formation of toxic endogenous protein aggregates. This inflammatory response can have beneficial effects by promoting tissue repair and the removal of cellular debris. However, it also results in the production of neurotoxic compounds that, in return, exacerbate neurodegenerative processes (Wyss-Coray and Mucke 2002; Glass et al. 2010). The response of the innate immune system includes immune cell activation and recruitment, phagocytosis of pathogens, clearance of cellular debris, and antigen presentation. It is well accepted that neuroinflammation is an underlying element of neurodegenerative disease such as ALS, AD, MS, and PD. To what extent central and peripheral immunity contribute to the development and progression of these diseases is not yet fully understood. This review will focus on CNS resident microglia and peripheral monocytes and give a broad overview over of what is known about their role in neurodegenerative diseases.

Microglia vs. monocytes: characterization and identity

Microglia are the brain's innate immune cells and are considered to be the first responders to CNS injury. However, in certain disease conditions, the blood–brain barrier (BBB) is disrupted, allowing the entry of peripheral immune cells from the bloodstream (Carvey et al. 2009). The contribution of microglia vs. peripheral monocytes in neuroinflammatory and neurodegenerative diseases is still a matter of debate. The investigations have been hampered by the inability to distinguish the two cell types, since both can give rise to inflammatory macrophages in the CNS and are morphologically indistinguishable. Many of the findings in the past few decades are based on markers that are expressed by both peripheral monocytes and microglia(i.e., Iba1, CD45, and CD11b) (Prinz et al. 2011; Greter et al. 2015). The distinction between resident microglia and infiltrating monocytes is critical to determine the characteristics of each disease, the involvement of both cell types, and the potential modulation of their immune response. Tables 1, 2 summarize common and newly

described markers for monocytes and microglia and how their expression profile change in neurodegenerative diseases.

In vivo studies of microglia and monocyte origin revealed that microglia and monocytes are ontogenetically distinct cells. Microglia are derived from hematopoietic progenitors in the yolk sac and invade the brain parenchyma around E9.5 during the murine CNS development (Ginhoux et al. 2010). In contrast, monocytes originate from the myeloid progenitor lineage in the bone marrow (Geissmann et al. 2010), where they are generated from dendritic cell and macrophage precursor cells (Geissmann et al. 2008). In mice, monocyte subsets were first identified by differential expression of chemokine receptor, CCR2. Later, they were characterized by their expression of the inflammatory marker Ly6C (Gr1) and it is now accepted that murine monocytes are divided into two major populations: $Ly6C^{high}$ and $Ly6C^{low}$ based on expression levels of Ly6C on the cell surface. In addition to Ly6C and CCR2 expression, $Ly6C^{high}$ cells were described as $CD11b^{+}/CD115^{+}/CCR2^{high}/CX3CR1^{low}$, whereas $Ly6C^{low}$ monocytes are $CD11b^{+}/CD115^{+/}CCR2^{low}CX3CR1^{high}$ (Geissmann et al. 2003; Gordon and Taylor 2005; Woollard and Geissmann 2010). Inflammatory $Ly6C^{high}$ monocytes represent approximately 2–5% of circulating blood cells in the periphery, which are actively recruited to sites of infection and inflammation (Serbina et al. 2008). $Ly6C^{low}$ patrolling resident monocytes are less abundant than $Ly6C^{Hi}$ monocytes where they adhere and migrate to luminal surfaces of blood vessels in a non-inflamed state (Auffray et al. 2007). Monocyte subsets in the human blood have different repertoires of surface receptors that may dictate functional roles. Human blood monocytes consist of two primary subsets with distinct expression profiles based on the LPS co-receptor, CD14 and the low-affinity IgG receptor, CD16. $CD14^{++}/CD16^{-}$ -monocytes, the most abundant in the human blood, are analogues of $Ly6C^{high}$ monocytes in mice and are referred to as “classical monocytes”. $CD14^{++}/CD16^{--}$ monocytes also express CCR2 similar to their murine counterparts (Geissmann et al. 2003). There is evidence that $CD14^{++}CD16^{+}$ monocytes equate to $Ly6C^{low}$ in mice based on gene expression profiles (Ingersoll et al. 2010).

Different approaches have been established to distinguish between resident microglia and recruited-blood monocytes. Microglia distinction was previously based on the expression levels of CD45, a protein tyrosine phosphatase expressed by myeloid cells. In microglia, CD45 is expressed at lower levels compared to other macrophages that are $CD45^{high}$. However, in disease, CD45 levels on microglia increase which makes them harder to distinguish from the recruited-blood monocytes (Ford et al. 1995). Recent developments in neuroimmunology, imaging, and genetics have greatly progressed our understanding of the unique nature of microglia in development, homeostasis, and disease, and have led to the identification of novel markers that are unique to resident microglia and have been used to distinguish them from bone marrow-derived macrophages (BMDM) and monocytic subsets. These markers include P2Y12, TMEM119, FCRLS, CX3CR1, Siglec-H, and olfactomedin-like 3 (Gautier et al. 2012; Chiu et al. 2013; Goldmann et al. 2013; Parkhurst et al. 2013; Yona et al. 2013; Butovsky et al. 2014; Bennett et al. 2016). However, similar to CD45, some of these markers may be modulated by activation and/or expressed in other cell types outside of the CNS and may not be suitable for unequivocally identifying or targeting tissue-resident microglia.

In addition to these novel markers, other methods have been developed to specifically target and manipulate microglia or macrophages. Initially, bone marrow chimeras were used to distinguish the two cell types. In this mouse model, fluorescently labeled bone marrow cells replace the original bone marrow cells after irradiation. This technique allows for tracking the origin and fate of infiltrating cells. This approach presents with some limitations, since the irradiation itself induces an opening of the BBB and the recruitment of monocytes to the CNS. It was demonstrated that CNS infiltration of peripheral monocytes is minimal if a head shield is used during irradiation (Ajami et al. 2007) or blood circulations are shared between GFP-positive and GFP-negative mice (Mildner et al. 2007). The latter method is termed ‘parabiosis’ and can also be used to distinguish microglia from monocytes. By combining mice that express different alleles of the CD45 gene (CD45.1 and CD45.2), Wang et al. (2016) analyzed infiltration of peripheral monocytes in mouse models of AD. Another important tool to study microglia vs. monocytes was the development of the CX3CR1-CreERT mouse (Jung et al. 2000), which takes advantage of the longevity of microglia compared to peripheral monocytes, that also express CX3CR1, but renew within a few weeks. This model is now used routinely to specifically target microglia.

With this in mind, it will be crucial to take advantage of and combine microglia-specific tools, such as transcriptomic profiles, proteomic signatures, and surface markers, to reduce the observation of artifacts arising from other myeloid cells (Gautier et al. 2012; Chiu et al. 2013; Goldmann et al. 2013; Parkhurst et al. 2013; Yona et al. 2013; Butovsky et al. 2014; Bennett et al. 2016).

Microglia vs. monocytes in amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by the loss of both upper and lower motor neurons leading to progressive skeletal muscle weakness and paralysis. Growing evidence has proven that non-neuronal cells directly contribute to motor neuron damage in ALS (Musaro 2010). Several studies in genetic models have well established that toxicity to motor neurons requires damage from mutant SOD1 acting within non-neuronal cells. Indeed, restricted expression of SOD1 mutations to neurons is not sufficient to induce ALS pathology (Pramatarova et al. 2001; Lino et al. 2002); however, wild-type neurons acquire an ALS phenotype when surrounded by glial cells carrying the SOD1 mutation (Clement et al. 2003).

In both animal models and ALS patients, neuronal loss is accompanied by a well-characterized neuroinflammatory reaction (McGeer et al. 1991; Kawamata et al. 1992; Engelhardt et al. 1993; Hall et al. 1998; Alexianu et al. 2001; McGeer and McGeer 2002), which includes proliferation of resident microglia (Henkel et al. 2004; Turner et al. 2004; Solomon et al. 2006; Appel et al. 2011). In ALS, microglia activation involves changes in morphology, gene expression, and surface receptors (Shibata et al. 2009; Butovsky et al. 2012, 2015). Microglia from mutant SOD1 mice (referred to hereafter as SOD1) display a phenotype that differs from both activation with LPS and the M1/M2 dichotomy (Chiu et al. 2013; Krasemann et al. 2017). Microglial activation in the spinal cord is an early event (Sanagi et al. 2010) that precedes clinical onset (muscle weakness), evidence of significant motor neuron loss, astrocyte reactivity (Alexianu et al. 2001), and increases with disease

progression (Hall et al. 1998; Elliott 2001; Olsen et al. 2001). Several studies have demonstrated that modulation of microglial response in SOD1 mice alters disease progression. SOD1-expressing microglia adopt a pro-inflammatory phenotype (Kobayashi et al. 2013), produce excessive reactive oxidative species (Harraz et al. 2008), and exhibit enhanced neurotoxicity after LPS treatment (Xiao et al. 2007) and in late phases of the disease (Liao et al. 2012), supporting the concept that microgliosis contributes to motor neuron degeneration. Consistent with these findings, inhibition of NF-κB suppresses the neuroinflammatory component of microglial toxicity in co-cultured motor neurons (Frakes et al. 2014), and deletion of galectin-3 exacerbates microglial activation and accelerates disease progression in SOD1 mice (Lerman et al. 2012). Another study demonstrated that a lack of IL-1β expression or treatment with IL-1β receptor antagonist extended the lifespan of SOD1 mice and attenuated the inflammatory pathology (Meissner et al. 2010). Moreover, deletion of SOD1 transgene within $CD11b^+$ myeloid cells (Boillee et al. 2006; Wang et al. 2009) improves survival in SOD1 mice. Others studies have shown the importance of CSF1R signaling in microglia and its contribution to neurodegeneration in SOD1 models (Gowing et al. 2009; Martinez-Muriana et al. 2016). However, it has also been proposed that microglia at pre-onset stage in SOD1 mice exhibit an anti-inflammatory phenotype (enriched for BDNF and CD163) and attenuate innate immune response compared with microglia at symptomatic stage (Liao et al. 2012; Gravel et al. 2016), supporting a trophic and neuroprotective role of microglia at the early phase of disease and a subsequent transformation with disease progression.

Studies in ALS patients have found that peripheral monocytes are functionally altered (Zhang et al. 2005, 2006; Nardo et al. 2011), skewed towards a pro-inflammatory state (Butovsky et al. 2015; Zhao et al. 2017), and can invade the CNS (Zondler 2016). Specifically, $CD14^+/CD16^-$ inflammatory monocyte levels in blood correlate with functional score in ALS (Murdock et al. 2016). Monocytes from rapidly progressive patients have a more inflammatory profile than monocytes from slower progressing patients (Zhao et al. 2017). Analogous changes are seen in SOD1 mice, even before the symptomatic onset of disease, defined by the appearance of tremors and the hind limb splay defect, and their degree of activation correlates with disease progression (Butovsky et al. 2012). Furthermore, myeloid cells are increased in ALS and SOD1 spinal cords (Engelhardt and Appel 1990; Appel et al. 1993; Obal et al. 2001; McGeer and McGeer 2002; Wilms et al. 2003; Henkel et al. 2004; Chiu et al. 2009; Butovsky et al. 2012). One hypothesis is that disruptions in the BBB (Evans et al. 2013) might facilitate the migration of peripheral monocytes to the CNS (Butovsky et al. 2012; Zondler 2016). In human patients, the levels of $CD14^+$ monocytes in the blood are decreased during early disease, indicating potential recruitment to the CNS (Mantovani et al. 2009). Several groups also described abnormal levels of pro-inflammatory cytokines in cerebral spinal fluid (CSF) and sera in patients with ALS (Simpson et al. 2004; Mitchell et al. 2009). Since microglia express high levels of CCL2 (Butovsky et al. 2012), which is also elevated in CSF of ALS patients (Nagata et al. 2007), and blood monocytes express higher levels of its receptor (Butovsky et al. 2012), a chemoattraction through the CCL2–CCR2 axis has been suggested to be responsible for recruiting inflammatory $Ly6C^+$ monocytes into the CNS (Mildner et al. 2007), possibly aggravating motor neuron injury. Importantly, blocking these infiltrating monocytes pharmacologically results in delayed

disease symptoms and extended survival in SOD1 mice (Butovsky et al. 2012). However, Zondler (2016) found that the presence of peripheral myeloid cells ($CD169^{+}$) in the spinal cord correlates with the number of surviving motor neurons in SOD1 transgenic mice, suggesting that peripheral macrophages may exert neuroprotection under certain conditions. Others have sustained that circulating monocytes do not contribute to spinal cord inflammation in ALS and have found that monocyte infiltration is limited to the peripheral nerves (Chiu et al. 2009; Graber et al. 2010; Lincecum et al. 2010). One justification for these inconsistent results is that the experimental paradigm of irradiation and bone marrow transplantation may introduce confounding variables that modify the natural course of the disease. Irradiation itself can provoke the entrance of cells in the CNS, most likely by altering the BBB tightness (Mildner et al. 2007), and introduces progenitor populations that are not in the blood under physiological circumstances (Ajami et al. 2007). Parabiosis experiments (surgically joining the circulatory systems of two organisms) between $SOD1^{G93A}$ and control mice expressing GFP in bone marrow cells and showed no evidence of infiltration into the CNS from periphery in parabiotic chimeras (Ajami et al. 2007). The limitation of this elegant approach, though, is that the donor cells were from naı¨ve wild-type mice. Hence, this paradigm does not account for the disease-associated dysregulation of peripheral inflammatory monocytes. These controversial results regarding the role of microglia and monocytes suggest their complex role in ALS and can be due to different experimental models (bone marrow transplantation studies, gene excision strategies, and pharmacological targeting of molecules) that are not easily comparable.

C9ORF72 expansion (DeJesus-Hernandez et al. 2011) is currently the most commonly demonstrated mutation related to ALS. Although its function is poorly understood, three independent studies shed light on its critical role in the immune system: *C9orf72* expression was highest in myeloid cells, and its loss led to lysosomal accumulation, myeloid expansion, altered immune responses in both macrophages and microglia, with age-related neuroinflammation (Burberry et al. 2016; O'Rourke et al. 2016), and signs of severe autoimmunity (Atanasio et al. 2016). Though the absence of neurodegeneration in these *C9orf72*-deficient mice provides an argument against the loss of *C9orf72* function as the sole driver of disease, these findings of altered myeloid cell function in C9orf72-deficient mice might support the possibility that abnormal immune responses play a fundamental role in ALS.

Facing such conflicting data on the effects of inflammation, between neuroprotection and neurotoxicity in ALS, a recent hypothesis suggests that the immune response in ALS occurs in two separate phases: protective in earlier stages and toxic in late stages of the disease (Appel et al. 2011; Hooten et al. 2015). This could explain the discrepancies that have been previously reported. The potential for different mechanisms underlying the immune response in disease initiation and progression has recently been proposed (Murdock et al. 2015). In SOD1 mice, a decrease in microglia number in the entire spinal cord was observed in the pre-symptomatic stage, suggesting a distinct microglial involvement in different stages of the disease (Gerber et al. 2012). During periods of slow disease progression, an anti-inflammatory process governs neuroinflammation, while in later phases of rapid progression, neuroinflammation is directed towards a strong inflammatory state (Liao et al. 2012). Most likely, microglia are the fulcrum of this complex immune response and drive the

polarization from one phase to the other during the course of the disease. Therefore, modulation of immune pathways may be more complex than anticipated. It remains for translational research studies of human ALS to document that both protective and toxic mechanisms are involved in the pathogenesis of the disease, and to employ such processes for therapeutic benefit.

Microglia vs. monocytes in Alzheimer's disease

Dementias affect approximately 47 million people worldwide, with Alzheimer's disease (AD) being the most common form of dementia (Prince et al. 2016). One of the major hallmarks of the disease is the extracellular accumulation of amyloid-beta (Aβ) protein as well as the development of intracellular neurofibrillary tangles (NFTs) comprised of hyperphosphorylated tau protein. Furthermore, AD pathology is accompanied by neuroinflammation, which also contributes to disease pathogenesis (Selkoe 2002; Zhang et al. 2013). Changes in cytokine levels are found in the CSF of individuals with mild cognitive impairment—amnestic type (MCI), who have an increased risk to develop AD, suggesting that this neuroinflammation occurs early in the disease development and might trigger AD (Tarkowski et al. 2003; Brosseron et al. 2014).

Recent GWAS studies identified variants of the myeloid cell genes Triggering receptor expressed on myeloid cells 2 (TREM2), CD33, and complement receptor 1 (CR1) to be associated with an increased risk to develop AD (Bradshaw et al. 2013a, b; Guerreiro et al. 2013; Jonsson et al. 2013), shifting the focus on resident microglia and peripheral myeloid cells. In addition, reactive myeloid cells accumulate specifically around Aβ-plaques in the brains of AD mouse models and humans. These findings are based on the usage of the common myeloid marker Iba-1, which raised the question whether these cells are actually resident microglia or peripheral myeloid cells that infiltrated the brain parenchyma during the development of the disease. Several studies suggested that there is a recruitment of peripheral myeloid cells to the AD brain. However, these studies have been conducted using bone marrow chimeras. Another study described the peripheral origin of plaque associated myeloid cells based on the microglial marker P2Y12 (Jay et al. 2015). However, this molecule is downregulated by reactive microglia as they can be found around amyloid plaques (Haynes et al. 2006; Krasemann et al. 2017). A study by Michaud et al. (2013) has suggested that peripheral myeloid cells do not actually infiltrate the brain parenchyma, but that their role is the removal of vascular Aβ from within the lumen of veins. As discussed above, Wang et al. (2016) distinguished microglia and monocytes by parabiosis of mice expressing either CD45.1 or CD45.2. Their study showed that there is no significant recruitment of peripheral monocytes to Aβ-plaques in the analyzed mouse models. This controversy emphasizes the need for a marker that can distinguish resident microglia from peripheral myeloid cells, regardless of the activation status. It remains a possibility that peripheral myeloid cells can be guided to the brain to help the resident microglia clear up amyloid plagues, yet conflicting reports exist as to whether they are capable of this. The approach of a transient depletion of resident microglia using an inducible suicide gene and their subsequent replacement with peripheral myeloid cells did not have any impact on Aβ plaque burden or APP processing (Prokop et al. 2015; Varvel et al. 2015). Conversely, intravenous infusion of monocytes from young mice at least transiently improved memory

function and reduced Aβ plaque burden (Hohsfield and Humpel 2015). Another group did not see an effect of injected monocytes alone, but when these monocytes were genetically engineered to express neprilysin, an Ab degrading enzyme, amyloid deposition was arrested (Lebson 2010).

Similar to the conflicting evidence of the role of monocytes in AD pathology, the question also remains as to the degree of involvement of resident microglia cells in the emergence and progression of AD. As previously discussed, variants of microglial genes like *TREM2*, *CD33*, and *CR1* are risk factors for AD and have become the focus of many studies. TREM2 is a transmembrane glycoprotein that binds phospholipids present in the brain due to neuronal cell death or myelin damage (Wang et al. 2015b) and has been shown to bind ApoE (Apolipoprotein E) (Atagi et al. 2015), whose isoform ε4 is a major risk factor for AD (Corder et al. 1993). We recently identified a TREM2-dependent pathway, which induces ApoE signaling in microglia. The TREM2-APOE pathway suppresses the homeostatic microglial signature and induces a transcriptional signature that is common in neurodegenerative diseases (Krasemann et al. 2017). This microglia phenotype switch is triggered by phagocytosis of dying neurons and, therefore, is specifically associated with neuritic Aβ-plaques in mouse and human AD. *Trem2* deficiency in APP-PS1 mice restored the microglial homeostatic signature, decreased clustering of microglia around Aβ-plaques, and reduced Aβ-plaque burden at early stages of the disease (Jay et al. 2015; Krasemann et al. 2017). However, at later stages, *Trem2* deficiency exacerbated the pathology (Wang et al. 2015b; Jay et al. 2017), indicating that TREM2 might have contrasting roles during different stages of the disease. Yuan et al. (2016) dissected the effect of *Trem2* deficiency in AD mouse models and TREM2 variants in human cases on the structure of Aβ-plaques and axonal dystrophy, and found that both in mice and humans, plaques are more filamentous and less compact, which leads to increased axonal dystrophy. A recent study analyzing soluble TREM2 (sTREM2) in the CSF of patients with different disease stages of AD, from preclinical to dementia stages, revealed that sTREM2 is already upregulated in the early stages of the disease and is associated with neuronal injury markers (Suarez-Calvet et al. 2016). This may reflect an early response of microglia to neuronal injury. TREM2 has also been shown to be modulated by the CD33 AD risk allele, another risk factor for late-onset AD (Bradshaw et al. 2013a, b; Chan et al. 2015). This study found that TREM2 expression is increased in monocytes from carriers with the CD33 risk allele and that CD33 expression itself is increased on microglia in human AD brains, and elevated levels of CD33 inhibited microglial uptake and phagocytosis of Aβ (Bradshaw et al. 2013a, b; Griciuc et al. 2013).

The complement system has also been demonstrated to play an important role in microglia response to Aβ. Microglia are responsible for complement-mediated synaptic loss (Hong et al. 2016), which can be rescued by deleting complement factors C1q, C3, or CR3 in a mouse model of AD (Maier et al. 2008; Shi et al. 2017). In spite of this specific response to amyloid, microglia are not able to halt disease progression. This might be because they are impaired in their phagocytic function by the presence of Aβ, chronic inflammation, or an age-linked dysfunction (Streit et al. 2004; Hickman et al. 2013; Krabbe et al. 2013). This functional impairment as well as their secretion of various pro-inflammatory cytokines in response to Ab (Vom Berg et al. 2012; Heppner et al. 2015; Wang et al. 2015a) led to the assumption that inhibition of the microglial reaction could ameliorate the pathology. Two

different approaches were used to test whether complete depletion of microglia would impact disease progression. Firstly, Grathwohl et al. (2009) demonstrated that depletion of microglia using the herpes simplex virus thymidine kinase (HSVTK) suicide gene had no effect on plaque pathology or neuritic dystrophy in APP-PS1 and APP23 mice. Secondly, treatment of AD mice with a CSF1-receptor antagonist to deplete microglia (PLX3397 or GW2580) reduced neuronal loss and improved cognition, but did not affect amyloid-plaque burden (Dagher et al. 2015; Olmos-Alonso et al. 2016; Spangenberg et al. 2016).

Multiple studies have aimed at modulating the cytokine profile in the brains of AD mice. Among them, Heneka et al. (2013) described that reduction of IL-1β through deletion of the NLRP3 inflammasome decreased Aβ and had a protective effect on memory. Inhibiting the IL-12/23 pathway similarly reduced AD-like pathology (Vom Berg et al. 2012). On the other hand, overexpression of IL-6 in AD mice attenuated plaque deposition and enhanced microglia-mediated phagocytosis of Aβ in vitro (Chakrabarty et al. 2010). Deficiency in the anti-inflammatory cytokine IL-10 increased microglial phagocytosis and reduced Aβ-plaque pathology (Guillot-Sestier et al. 2015). Taken together, it should be acknowledged that the response of microglia in AD is complex and graded (Raivich et al. 1999) and not solely ‘good’ or ‘bad’.

Microglia vs. monocytes in Parkinson’s disease

Parkinson’s disease (PD) is the second most common neurodegenerative disease in the aging population (Pringsheim et al. 2014). It is a chronic progressive disease characterized by cytoplasmic aggregates of Lewy bodies comprised of α-synuclein and ubiquitin. Progressive degeneration and ultimately the loss of dopaminergic neurons in the *substantia nigra pars compacta* (SNpc) lead to a decrease in dopamine levels which manifest as the motor symptoms associated with PD such as tremors, rigidity, gait dysfunction, and bradykinesia (Hornykiewicz and Kish 1987). In addition to progressive neurodegeneration, inflammation plays a central role in the pathophysiology of the disease. As with many neurodegenerative diseases, the current underlying pathological mechanisms that lead to neuronal cell loss/death, neuroinflammation, and motor impairment remain elusive. Insight in the pathological mechanisms of PD has largely stemmed from animal models incorporating toxins such as neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in mice and 6-hydroxydopamine (6-OHDA) in rats/monkeys or genetic-based models using α-synuclein or LRRK2, and PARKIN gene modifications (Dauer and Przedborski 2003; Blesa and Przedborski 2014).

Immune system involvement in PD was demonstrated by the observation of elevated pro-inflammatory mediators (TNFα, IL1β, and IL6) in the CSF and brains of PD patients (Mogi et al. 1994a, b). McGeer et al. (1988) showed for the first time that reactive microglia are evident in the *SNpc* of human post-mortem tissue, suggesting that neuroinflammation is an additional hallmark of PD. In addition, positron emission tomography (PET) studies have shown that microgliosis is a prominent feature in PD brains (Gerhard et al. 2006; Bartels et al. 2010). The role of microglia in PD was further strengthened by a GWAS study identifying a single nucleotide polymorphism (SNP) in the human leukocyte antigen gene (HLA-DRA), which is expressed by microglia, as a genetic risk factor for late-onset PD

(Hamza et al. 2010). Furthermore, the distribution of microglia, with the greatest density in the SN and striatum, leads to the assumption that microglia are involved in the disease development or progression or possibly both. In line with this, peripheral injections of LPS induced microgliosis and reduced tyrosine hydroxylase-positive neurons in the SN, illustrating that activation of microglia can indeed induce neurotoxicity in dopaminergic neurons (Qin et al. 2007; Bodea et al. 2014).

Reactive microglia have also been detected in the SN in toxin-induced as well as transgenic mouse models for PD (Czlonkowska et al. 1996; Sanchez-Guajardo et al. 2010; Hoenen et al. 2016). Furthermore, mice lacking the fractalkine receptor (CX3CR1), which is expressed by microglia and is important for microglia–neuron communication, show extensive neuronal loss in the toxin-induced MPTP PD mouse model (Cardona et al. 2006).

In addition to investigating the role of microglia, there have also been several efforts to study the peripheral immune system in PD. Elevated serum levels of cytokines (IL-6, IL-10, TNFα, and IFNγ) have been reported in peripheral blood from PD patients (Brodacki et al. 2008; Reale et al. 2009). A study by Lampe et al. showed higher expression levels of polymorphic major histocompatibility complex class II molecules, HLA-DR and HLA-DQ, expressed by monocytes in the CSF and peripheral blood of PD patients compared with healthy subjects, indicating that the peripheral immune system is activated in PD (Lampe et al. 2003).

Mutations in the leucine-rich repeat kinase 2 (LRRK2) gene are the most common cause of familial PD and a risk factor for sporadic PD. *Lrrk2* has been shown to be implicated in peripheral inflammation and is seen to be relatively abundant in mononuclear cells and macrophages in the periphery (Hakimi et al. 2011). GWAS studies revealed that LRRK2 modifications are associated with autoimmune diseases such as Crohn's disease, ulcerative colitis, and inflammatory bowel disease (Umeno et al. 2011). Likewise, LRRK2 expression is seen to be increased by pro-inflammatory mediators like IL-1β, TNFα, and IFN-γ (Gardet et al. 2010; Hongge et al. 2015). A study investigating the role of LRRK2 in monocyte dysregulation in PD reported elevated LRRK2 levels in both ($CD14^{dim}/CD16^{+}$ and $CD14^{++}/CD16^{-}$) monocyte subsets from PD patients in comparison to healthy controls (Bliederhaeuser et al. 2016). The increased LRRK2 expression level positively correlates with the frequency of inflammatory monocytes from PD patients (Cook et al. 2017). In addition, monocytes from PD patients display a distinct transcriptome signature, have an elevated inflammatory profile, and are "hyper-responsive" to LPS stimulation in comparison to healthy controls (Grozdanov et al. 2014). Thus, indicating that there is an underlying inflammatory reaction in the disease.

Similar to the situation in AD, it is still being debated whether these inflammatory monocytes can infiltrate the CNS in the context of PD. A study by Rodriguez et al. (2007) using a chronic toxin-induced MPTP PD model in GFP bone marrow chimeric mice suggests that BMDM enter the brain in their treatment paradigm. Using the same model with only a subchronic dose of MPTP, Depboylu et al. (2012) showed that these infiltrating cells are not involved in the disease development, since resident microglia are the major phagocytes of neuronal cell debris. Another study suggested that deletion of $CCR2^{+}$

monocytes in the MPTP model does not impact dopamine levels in the striatum (Kalkonde et al. 2007). Parillaud et al. also demonstrated that infiltrating CCR2^{+} monocytes in the acute MPTP model did not contribute to the dopaminergic neuronal loss (Parillaud et al. 2017). However, it was also demonstrated that BMDM, which were genetically engineered to over-express the neuroprotective glial cell line-derived neurotrophic factor (GDNF) were able to ameliorate MPTP-induced neurodegeneration (Biju et al. 2010), emphasizing the complexity of the immune and CNS involvement.

Taken together, these studies illustrate that microglia and peripheral myeloid cells are implicated in PD pathogenesis. Whether or not blood-borne monocytes infiltrate the CNS in this disease remains to be determined. Considering the evidence that circulating monocytes exhibit a hyper-activate inflammatory phenotype in PD, they may present as an attractive therapeutic target to attenuate the peripheral immune dysregulation in PD progression.

Microglia vs. monocytes in multiple sclerosis

Multiple sclerosis is a complex inflammatory autoimmune disease accompanied by focal plaques and demyelination in white matter brain regions and spinal cord (Symonds 1975; Compston and Coles 2002; Lassmann et al. 2007). MS is also considered in part to be a neurodegenerative disorder as axonal damage, cell loss, and degeneration are common pathological features, especially at late stages of the disease (Haines et al. 2011). The mechanism of MS pathology is elusive but is known to involve complex interactions between systems and cell types including neurons, glia, and immune cells accompanied by permeability of the BBB (Bruck et al. 1995). Supported by the main animal model of MS, the experimental autoimmune encephalomyelitis (EAE), MS was traditionally thought of as a predominantly T-cell-mediated autoimmune disease. Extrapolation of data from EAE studies translating to MS clinical trials has only been partially successful (Gold et al. 2006, Aharoni 2013), which could be in part to the inflammatory process in MS being driven by other immune cells (Cardona et al. 2008, Lassmann et al. 2012, Croxford et al. 2015).

A central role for inflammatory monocytes in disease progression has been demonstrated in EAE mouse models. Myeloid cells, particularly monocytes, infiltrate the CNS in the early stages of EAE development and contribute to the inflammatory response and clinical disease (Ajami et al. 2011; Mikita et al. 2011). Chemokine receptor CCR2 is critical for the accumulation of Ly6C^{high}/CCR2^{high} monocytes in the CNS. CCR2 and its ligand CCL2 play an important role in regulating Ly6C^{high}/CCR2^{+} Monocyte infiltration to the CNS and facilitate tissue damage in MS and EAE (Mildner et al. 2007, 2009; King et al. 2009). In EAE, monocytes that are recruited to the CNS are CCR2^{high}/CX3CR1^{low} (Saederup et al. 2010; Garcia et al. 2013), further distinguishing them from resident microglia. Patients with MS display high levels of monocyte-secreted inflammatory molecules in serum compared to healthy individuals, demonstrating a role for peripheral monocytes in disease progression. For example, increased levels of serum TNFα and α have been reported with the onset of MS relapse (Rudick and Ransohoff 1992; Imamura et al. 1993; Huang et al. 2004). The inflammatory profile of monocytes from patients with MS can vary greatly between MS type, disease severity, and gender (Kallaur et al. 2013). Infiltrating monocytes are abundant

in active MS lesions and are associated with demyelination (Bruck et al. 1995; Lucchinetti et al. 2000).

This active demyelination and neurodegeneration is also associated with reactive microgliosis (Lassmann 2014). Due to the difficulty in distinguishing monocytes and microglia both morphologically and functionally, the complex roles of microglia vs. monocytes in the inflammatory/degenerative cascade in MS have yet to be fully revealed. However, with the advancement of specific markers and identification of molecular signatures of these cells, significant advancements are being made in this field (Chiu et al. 2013; Hickman et al. 2013; Butovsky et al. 2014). Microglia and macrophages accumulate in active sites of demyelination and neurodegeneration in MS. A recent comprehensive study of microglia and macrophage phenotypic differences used novel cell-specific markers to investigate these phagocytes over different stages of MS (Zrzavy et al. 2017). On one hand, they demonstrate that the homeostatic microglia marker P2Y12 is lost in active MS lesions, but reappears in inactive lesions. On the other hand, they used the marker TMEM119, which is expressed on microglia, but not on infiltrating monocytes, to distinguish phagocytic cells within the active lesion (Butovsky et al. 2014; Bennett et al. 2016; Satoh et al. 2016). With the use of this marker, they demonstrated that the majority of cells associated with active demyelination originate from resident microglia, indicating that microglia play a central role in MS disease progression (Zrzavy et al. 2017).

Earlier studies have described that reactive microglia are present at early and late stages of disease (van der Valk and Amor 2009; Singh et al. 2013). They are present in demyelinating lesions (Ponomarev et al. 2005) and correlate with the axonal and oligodendrocyte pathology (Trapp et al. 1998; Henderson et al. 2009). Experiments using bone marrow chimeric mice showed that microglial activation even occurs before the onset of EAE (Ponomarev et al. 2005). Once microglia are activated, they can damage other CNS cells, in particular oligodendrocytes and neurons (Butovsky et al. 2006a, b; Peferoen et al. 2014). Microglia in MS contain myelin and axonal debris, present higher expression of MHC class II and co-stimulatory molecules, and secrete different inflammatory and neurotoxic mediators in lesions (Boven et al. 2006; Butovsky et al. 2006a, b; Huizinga et al. 2012; Vogel et al. 2013). Depletion of microglia using the herpes simplex virus thymidine kinase (HSVTK) suicide gene attenuated disease severity and demyelination in EAE (Heppner et al. 2005). Similarly, microglia-specific deletion of transforming growth factor (TGF)-β-activated kinase 1 (TAK) with the use of the CX3CR1-CreERT2 mouse model reduced CNS inflammation and myelin damage (Heppner et al. 2005; Ponomarev et al. 2005; Goldmann et al. 2013).

These studies show that microglia can promote disease progression in EAE and MS. Pre-active lesions, which are clusters of activated microglia in the white matter of MS patients, develop without demyelination and peripheral cell infiltration (De Groot et al. 2001) and thus may represent the early stage of inflammatory lesions (van Noort et al. 2011). However, microglia also can be neuroprotective and promote CNS repair by the clearance of inhibitory myelin debris (Miron et al. 2013; Lampron et al. 2015). Furthermore, IL-4- or IFNγ-stimulated microglia promote oligodendrogenesis and neurogenesis (Butovsky et al. 2006a,

b). These studies demonstrate the fine balance between neuroprotection and neurotoxicity effects of microglia in EAE.

Homozygous mutations in TREM2, a myeloid cell-surface receptor which is also implicated in AD, lead to demyelination and early onset dementia in humans (Paloneva et al. 2002). In the cuprizone-induced mouse model of demyelination, *Trem2* deficiency rendered microglia defective in clearing myelin debris, which resulted in a persistent demyelination (Cantoni et al. 2015; Poliani et al. 2015). Thus, microglial reaction after inflammatory and neurodegenerative signals depends on a fine-tuning of immunomodulatory mediators and microglia phenotypes.

A study using the $CCR2^{RFP}$–$CX3CR1^{GFP}$ mouse model demonstrated distinct roles for microglia and infiltrating monocytes during EAE. In this model, recruited monocytes are associated with nodes of Ranvier and initiate demyelination, whereas microglia appear to clear debris (Yamasaki et al. 2014). The mechanism of recruitment remains relatively elusive with some studies demonstrating that it is the “activation” of resident microglia that may represent one of the initial steps in EAE pathogenesis, preceding and possibly triggering the infiltration of bloodderived cells (Zrzavy et al. 2017). Yamasaki et al. (2014) present divergent molecular and functional signatures of both cell types, which are maintained during neuroinflammation. These characteristic signatures reflect ontogenic differences between microglia and blood-borne monocytes and strongly argue for cell-specific neurotoxic and protective properties in neuroinflammatory disorders.

Conclusion

Microglia and monocytes have recently been in the spotlight when discussing CNS pathologies. In the healthy body, these cells exist in parallel systems; however, during disease, their paths might cross (King et al. 2009; Shi and Pamer 2011). As described here, both central and peripheral immune responses contribute to the development and progression of many neurodegenerative diseases. As emphasized throughout this review, the complex roles of microglia vs. monocytes in these diseases have yet to be fully revealed due to the difficulty of distinguishing these cell types both morphologically and functionally.

Over the past decade, several tools have been developed to distinguish microglia and peripheral monocytes. As described in the introduction, one widely used tool has been bone marrow chimeras. However, the irradiation needed to generate these mice leads to BBB damage and subsequent monocytes infiltration into the CNS, which would otherwise not occur. This method was improved by introducing head shields to protect the BBB. As an alternative to bone marrow chimeras, parabiosis, which allows for a shared blood circulation between two mice, can be used to distinguish resident microglia and peripheral monocytes (Hashimoto et al. 2013; Wang et al. 2016). Additional tools have been developed to specifically target microglia, such as the *Cx3cr1*-Cre/ERT mouse model. With these models, however, it has to be kept in mind that peripheral monocytes will be affected too and only the Cre-inducible model, not the constitutive model, can target microglia alone. Recently, the *Sall1*-Cre mouse has been proposed as an alternative to *Cx3cr1*-Cre with the advantage of targeting only resident microglia and not peripheral monocytes (Buttgereit et al. 2016).

The description of specific markers and identification of molecular signatures of these cells has helped to generate significant advancements in this field (Chiu et al. 2013; Hickman et al. 2013; Butovsky et al. 2014). Transcriptomic gene assays and computational biology, along with proteomic and epigenomic analysis, have provided unbiased insights into the contextual factors driving authentic, in vivo microglial reaction states (Gosselin et al. 2014; Matcovitch-Natan 2016; Gosselin et al. 2017). These new tools will also be helpful in answering the question of whether peripheral monocytes migrate to the CNS during certain neurodegenerative diseases and to further distinguish the distinct roles of microglia and monocytes. In this context, the fate of infiltrating monocytes also has to be taken into consideration. Either their appearance in the CNS is just transient (Ajami et al. 2011) or they could be reprogrammed by their new environment and become more like microglia, making them harder to distinguish (Gosselin et al. 2014; Lavin et al. 2014; Varvel et al. 2015). Either way, their role in neurodegenerative diseases might be restricted to the short time that they are present in the CNS as a distinct cell type.

Approaches using genetically engineered cells to deliver neuroprotective molecules as demonstrated in a mouse model of PD might be an interesting therapeutic option. Specific targeting and modulation of resident microglia and peripheral myeloid cells in combinatorial manner could potentially alleviate disease progression. Assuming that immune cells infiltrate the CNS, diminishing the immune response in the periphery may have beneficial outcomes and specific targeting of the peripheral immune system may lead to new avenues of therapeutics to rescue CNS homeostasis, restore function, and reduce inflammatory burden. The recent development of cell-specific markers in combination with the modern imaging advances such as PET to distinguish between functionally different resident and infiltrating cells could prove to be highly beneficial. It is important to keep in mind, however, that it is not fully understood whether the immune responses in CNS diseases are detrimental or beneficial. As we have discussed in this review, the microglia and monocyte response could be both neuroprotective and neurotoxic depending on the stage and progression of the disease. There is a fine balancing act between both states, and a microglia and/or monocyte reaction in neurodegenerative diseases may “tip the balance” toward a ‘good’, ‘bad’ or ‘neither’ response. Therefore, modulation of the immune pathways may be more complex than anticipated and timing of therapeutic intervention may be pivotal.

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Table 1

Microglia markers in health and disease

Microglia	Markers	References
Homeostatic	Cd11b^{+}	Hickman et al. (2013), Butovsky et al. (2014), Asai et al. (2015), Greenhalgh et al. (2016), Zrzavy et al. (2017)
	Cd45^{low}	
	Cx3cr1^{+}	
	F4/80^{+}	
	Fcrls^{+}	
	Iba1^{+}	
	Olfml3^{+}	
	P2ry12^{+}	
	Sall1^{+}	
	Siglec-H^{+}	
	Tmem119^{+}	
	Tgfbr^{+}	
	Csf1r^{+}	
Neurodegenerative diseases	Arg1↑	Chiu et al. (2013), Holtman et al. (2015), Keren-Shaul (2017), Krasemann (2017), Zrzavy et al. (2017)
	Apoe ↑	
	Axl ↑	
	Ccl2 ↑	
	Cd45 ↑	
	Clec7a ↑	
	Gpnmb ↑	
	Msr1↑	
	Spp1↑	
	Cd11b →	
	F4/80 →	
	Fcrls →	
	Iba1 →	
	Tmem119 →	
	Csf1r↓	

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Microglia	Markers	References
	P2ry12 ↓	
	Siglec-H ↓	
	Sall1 ↓	
	Tgfbr↓	

Arrows indicate changes in expression: ↑ increased, ↓ decreased, → unchanged

Table 2

Monocyte markers in health and disease

Monocyte subsets	Markers	References
Classical inflammatory	$Ccr2^{high}$	Mildner et al. (2007, 2009), Ingersoll et al. (2010), Butovsky et al. (2012), Rose et al. (2012), Asai et al. (2014)
	$Cd11b^{+}$	
	$Cd115^{+}$	
	$Cd169^{+}$	
	$Cd43^{+}$	
	$Cd45^{high}$	
	$Cx3cr1^{low}$	
	$Iba1^{+}$	
	$Ly6c^{high}$	
	$Ly6g^{neg}$	
Patrolling	$Ccr2^{low}$	Auffray et al. (2007), Ingersoll et al. (2010), Rose et al. (2012), Carlin et al. (2013), Michaud et al. (2013)
	$Cd11a^{+}$	
	$Cd11b^{+}$	
	$Cd115^{+}$	
	$Cd45^{high}$	
	$Cx3cr1^{high}$	
	$Iba1^{+}$	
	$Ly6c^{low}$	
	$Cd83^{+}$	
	$Cd16^{+}$	
	$Cd36^{+}$	
	$Cd274^{+}$	

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