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Let's make microglia great again in neurodegenerative disorders

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Abstract

All of the common neurodegenerative disorders–Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS) and prion diseases (PrD)–are characterized by accumulation of misfolded proteins that trigger activation of microglia; brain-resident mononuclear phagocytes. This chronic form of neuroinflammation is earmarked by increased release of myriad cytokines and chemokines in patient brains and biofluids. Microglial phagocytosis is compromised early in the disease process, blocking clearance of abnormal proteins. This review identifies immune pathologies shared by the major neurodegenerative disorders. The overarching concept is that these aberrant innate immune pathways can be targeted for return to homeostasis in hopes of coaxing microglia into clearing neurotoxic misfolded proteins.

Keywords

Neurodegenerative diseases; proteinopathy; microglia; phagocytosis; neuroinflammation; innate immunity

1. Introduction

The most common neurodegenerative disorders, Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS) and prion disease (PrD) are triggered by accumulation of abnormally folded proteins that self-assemble into β-sheet structures and aggregate in the central nervous system (CNS). Interestingly, whether owed to sporadic, genetic or infectious etiologies, these abnormal proteins share "prion-like" characteristics, including their propensity for spreading (Vincent et al. 2008; Lee and Kim 2015; Hock and Polymenidou 2016; Goedert et al. 2016; Braak and Del Tredici 2016). Another key feature of these diseases is chronic neuroinflammation accompanied by neuronal injury and loss, leading to cognitive and/or motor deficits. While once regarded as epiphenomenon, there is now good evidence suggesting that inflammation and the immune response play fundamental roles in neurodegenerative disorders (López González et al. 2016). In this review, we will consider immune and inflammatory mechanisms implicated in AD, PD, ALS

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and PrD. Rather than exhaustively cataloguing the features specific to each disease, we broadly define pathologies of each neurodegenerative disorder in Table 1. In this review, we discuss the immunopathological similarities shared by these diseases in hopes of identifying future therapeutic target(s).

2. Pathogenic protein accumulation and spreading: contribution of exosomes

Exosomes are lipid bilayer endosome-derived nanovesicles mediating intercellular communication. In the CNS, exosomes encapsulate proteins, RNAs and miRNAs and are released by neurons, astrocytes, oligodendrocytes and microglia (the brain resident mononuclear phagocytes) (Bobrie et al. 2011; Hannafon and Ding 2013), where they are thought to mediate neuron-glia communication insuring neuronal development and health (Antonucci et al. 2012; Frühbeis et al. 2013a; Frühbeis et al. 2013b; Fröhlich et al. 2014). Internalization of exosomes is triggered by the interaction of various proteins and lipids with receptors on the target cell to initiate endocytosis (Morelli et al. 2004). Phagocytic cells uptake exosomes via phagocytosis or micropinocytosis (Feng et al. 2010; Fitzner et al. 2011), while non-phagocytic cells rely on clathrin-dependent and -independent endocytosis (Escrevente et al. 2011; Svensson et al. 2013).

Exosomes have been isolated from the human brain and cerebrospinal fluid (CSF) under both physiological and pathological conditions (Vella et al. 2008; Street et al. 2012). In neurodegenerative diseases, the presence of exosomes packed with abnormal or misfolded proteins suggests that the exosomal machinery is responsible for cell-to-cell “spreading” (Aguzzi and Rajendran 2009; Rajendran et al. 2014). Interestingly, exosomal spreading of misfolded proteins was first described for propagation of prions in cellular bioassays (Fevrier et al. 2004; Vella et al. 2007; Coleman et al. 2012) and in prion-infected mouse brains (Arnold et al. 1995; Alais et al. 2008). Importantly, those early discoveries showed that PrP^{Sc} containing exosomes were infectious *in vitro* and *in vivo* (Fevrier et al. 2004; Vella et al. 2007; Alais et al. 2008); spurring the study of exosomes in other neurodegenerative diseases.

In the context of AD, exosomal transmission has been described for Aβ trafficking in mice brains (Kokubo et al. 2005), and other reports suggest that exosomes may facilitate uptake and degradation of Aβ by microglia (Bulloj et al. 2010; Tamboli et al. 2010; Yuyama et al. 2012). Additionally, exosome-mediated trafficking of Aβ and phosphorylated tau has been observed in human brains and CSF samples (Rajendran et al. 2006; Sharples et al. 2008; Saman et al. 2012). Cell-to-cell tau propagation occurs *in vitro* (Frost et al. 2009) and *in vivo* (Polanco et al. 2016), and both inhibition of exosome biosynthesis and depletion of microglia halts tau spreading in a mouse model of tauopathy (Asai et al. 2015). One could conclude from these studies that microglia phagocytose exosomal tau secreted from neurons and subsequently release tau-containing exosomes, further spreading tau pathology.

Exosomes containing monomeric and oligomeric α-synuclein have been found at increased abundance in PD patient plasma and CSF (Emmanouilidou et al. 2010; Yang et al. 2015; Stuendl et al. 2016; Luo et al. 2016). Additionally, exosome-mediated secretion of α-

synuclein and transmission from cell-to-cell has been demonstrated *in vitro* (Alvarez-Erviti et al. 2011b; Danzer et al. 2012) and *in vivo* (Kong et al. 2014; Tsunemi et al. 2014). These enigmatic structures also seem to accelerate α-synuclein aggregation (Grey et al. 2015; Stuendl et al. 2016), and may contribute to inclusion formation and neuronal cell death (Desplats et al. 2009).

Misfolded superoxide dismutase 1 (SOD1) and TAR DNA-binding protein 43 (TDP43) associated with ALS have also been found within exosomes (Gomes et al. 2007), and mutant SOD1 aggregates can propagate between cells via this mechanism (Münch et al. 2011; Münch and Bertolotti 2011). This suggests a role for exosomes in the intercellular spreading of abnormal proteins in ALS (Nonaka et al. 2013; Grad et al. 2014). Similarly, exosomal spreading of dipeptide repeat proteins (DPRs), characteristic of ALS and frontotemporal dementia (FTD), has been demonstrated *in vitro* (Ding et al. 2015; Westergard et al. 2016).

However, the source of exosomes carrying abnormal proteins is still unclear, as both neurons and reactive microglia reportedly release exosomes (Tamboli et al. 2010; Yuyama et al. 2012). Moreover, exosomes shed from peripheral mononuclear phagocytes in the circulation have the ability to cross the blood-brain barrier (BBB) and exert their effects in the CNS (Alvarez-Erviti et al. 2011b; Couch et al. 2011). This latter finding highlights the importance of understanding the influence of peripheral mechanisms on neurodegenerative diseases.

3. Exosomes as immune modulators

Aside from their role in spreading pathogenic proteins, exosomes are involved in modulating immune and inflammatory processes within the CNS. Indeed, various cell types involved in brain inflammation communicate by shedding exosomes that help to initiate and propagate inflammatory responses. In another disease paradigm–cancer, exosomes have a role in antigen cross-presentation by transferring antigens from tumor cells to dendritic cells, where they present antigen to T cells (Zitvogel et al. 1998; Wolfers et al. 2001) and exhibit other immune properties (Iero et al. 2008; Théry et al. 2009).

In AD brains, reports indicate increased levels of heat shock protein 72 (HSP72) (Hondius et al. 2016), which induces inflammation through exosomal release (Anand et al. 2010; Heppner et al. 2015). In the context of PD, astrocytes and microglia internalize cytotoxic α-synuclein, further promoting inflammation via release of exosomes containing inflammatory mediators in association with production of reactive oxygen species including nitric oxide free radical (Lee et al. 2008; Lee et al. 2010; Alvarez-Erviti et al. 2011a; Vekrellis et al. 2011). Another report indicates that α-synuclein induces production of major histocompatibility class II and tumor necrosis factor (TNF)-containing exosomes by microglia; triggering neuronal death and reinforcing the vicious cycle of neuroinflammation in PD (Chang et al. 2013).

Exosomes are highly enriched in mRNAs and small RNAs such as piwi-interacting RNA (piRNA), miRNA and tRNA transcripts (Valadi et al. 2007; Bellingham et al. 2012; Cheng et al. 2014a; Cheng et al. 2014b). Release of exosomes into biological fluids allows for small RNA transcripts to be taken up by target cells that modulate gene expression (Alvarez-Erviti

et al. 2011c). Animal studies show that specific miRNAs can activate microglia associated with prion lesions (Saba et al. 2008; Montag et al. 2009; Saba et al. 2012). Furthermore, miRNA profiles are altered in exosomes isolated from CSF, blood and brains from AD (Cogswell et al. 2008; Kumar et al. 2013; Grasso et al. 2014; Gui et al. 2015), PD (Junn et al. 2009; Maciotta et al. 2013; Gui et al. 2015), and ALS patients (Gui et al. 2015). In AD patients' CSF and brains, modulation of miRNA clusters correlates with change in genes involved in amyloid precursor protein (APP) processing (Hébert et al. 2008) and synaptic plasticity (Sarkar et al. 2016). Moreover, aberrantly expressed messenger and long non-coding RNAs discovered in CSF exosomes may be pathogenic in the PD context (Gui et al. 2015). For example, miRNAs have been shown to mediate both oxidative stress and injury to dopaminergic neurons associated with abnormal α-synuclein (Junn et al. 2009; Cho et al. 2013). It is interesting to note that in ALS, expression of several miRNAs involved in the immune response is elevated in the diseased spinal cord (Zhou et al. 2013), and miRNA-mediated Toll-like receptor (TLR) activation has been documented in both AD (Lehmann et al. 2012) and PD (He et al. 2014). This set of findings is given even more weight as TLR activation is strongly involved in immune responses during the course of neurodegenerative diseases (see section 4 below) (Letiembre et al. 2009; Zhao et al. 2010; Béraud et al. 2011; Lehmann et al. 2012; Noelker et al. 2013).

4. Receptor-mediated innate immune activation

Glial activation, including reactive microgliosis, is a common trait in neurodegenerative diseases, although the particular neuroinflammatory phenotype varies with the type of CNS pathology (Heppner et al. 2001; Sargsyan et al. 2005; Long-Smith et al. 2009; Prokop et al. 2013). Microglial activation in neurodegenerative disorders is sometimes accompanied by reactive astrocytes, lymphocytes and macrophages infiltrating from the periphery (Graves et al. 2004; Gate et al. 2010; Lewis et al. 2012). Activation of mononuclear phagocytes (microglia and hematogenous macrophages) and subsequent release of inflammatory mediators is often mediated by receptors; in the context of neurodegenerative diseases, the TLR family is particularly involved. Polymorphisms reducing the activity of TLR4 occur more frequently in AD patients than in healthy controls (Minoretti et al. 2006; Wang et al. 2011). Expression of TLR2, TLR4 and its co-receptor (CD14) are increased in AD patient brains (Fassbender et al. 2004; Liu et al. 2005; Walter et al. 2007; Letiembre et al. 2009). Remarkably, plaque-associated microglia have increased mRNA expression for TLR2 and TLR4 in a mouse model of cerebral amyloidosis (Frank et al. 2009). One study suggests that a physical interaction is required amongst CD14, TLR2 and TLR4 for stimulation of microglial responses by fibrillar Aβ (Reed-Geaghan et al. 2009). Other animal studies support a beneficial role for TLR2/4 activation in AD pathophysiology through amyloid-β (Aβ) phagocytosis (Tahara et al. 2006; Glass et al. 2010; Michaud et al. 2013), via blocking acute Aβ oligomer-mediated glial activation and memory impairment in APP/PS1 mice (Balducci et al. 2017). Stimulation of TLR4 was also reported to be beneficial by attenuating tauopathy in human tau transgenic mice (Qin et al. 2016). However, a contradictory report showed that deletion of the downstream TLR mediator, interleukin-1 receptor-associated kinase (IRAK) 4, increased Aβ clearance while reducing gliosis (Cameron et al. 2012), and a second set of findings showed that inhibition of TLR2 activation in APP/PS1 mice resulted

in reduced gliosis and Aβ burden associated with learning improvement (McDonald et al. 2016). One possible explanation for this discordancy is use of different rodent models that develop different diseases with varying kinetics.

Interestingly, TLR4 is elevated in brains of patients suffering from α-synucleopathies (Letiembre et al. 2009) and in PD mouse models, where its ablation impairs phagocytic uptake of α-synuclein and enhances neurodegeneration (Cookson 2009; Stefanova et al. 2011; Fellner et al. 2013). In addition, the TLR4 pathway has been shown to regulate PARK2 transcription in mononuclear phagocytes (Tran et al. 2011) and a polymorphism in CD14 is a risk factor for late-onset PD (Wahner et al. 2007; Deleidi and Gasser 2013). These data begin to suggest a beneficial role for TLR4 in PD by mediating microglial clearance of α-synuclein. TLR2 expression is increased in neurons and in microglia residing in disease-relevant PD brain areas and in transgenic Thy1.2-α-synuclein mouse brains (Doorn et al. 2014; Drouin-Ouellet et al. 2014; Dzamko et al. 2016). In addition, misfolded α-synuclein has been shown to increase expression of TLR2 and other TLRs and to activate microglia in culture (Béraud et al. 2011) and in mouse brains expressing human α-synuclein (Béraud et al. 2011; Kim et al. 2013). Misfolded α-synuclein seems to dually activate TLR1/2 signaling (Daniele et al. 2015), and recent data support the notion that neuron-secreted α-synuclein induces activation of TLR2 and subsequent inflammatory responses in microglia, causing neurodegeneration (Kim et al. 2016; Dzamko et al. 2016).

In similar fashion, TLR2 and TLR4 expression is increased in reactive microglia in the ALS spinal cord (Casula et al. 2011), and mutant SOD1 activates microglia via TLR2/4 and the CD14 co-receptor, potentiating neurotoxicty (Liu et al. 2009; Zhao et al. 2010). Strikingly, TLR4 antagonists rescued ALS mouse-derived neurons in culture (De Paola et al. 2016), while TLR4 deletion increased survival in ALS transgenic mice (Lee et al. 2015), suggesting that aberrantly elevated microglial TLR4 signaling contributes to ALS pathology.

With regard to prionopathies, dominant-negative TLR4 mice present with accelerated infection after PrP^{sc} inoculation (Spinner et al. 2008), while TLR2 deficiency switches prion-induced microglial activation from neurotoxic to neuroprotective (Wang et al. 2015a). On the other hand, TLR1/2 expression is responsive to recombinant prion fibrils in mixed neuronal/glial cultures, and glial activation inhibits prion replication (Kang et al. 2016). Altogether, these studies highlight the role of TLR-dependent innate immune activation and its interference with PrP infection.

Immune receptors other than TLRs have been found to incur risk for neurodegenerative disorders (Doty et al. 2014). Triggering receptor expressed on myeloid cells 2 (TREM2) took the field by storm after genome-wide association studies (GWAS) identified rare variants as risk factors for AD (Guerreiro et al. 2013; Jonsson et al. 2013; Lill et al. 2015), PD (Rayaprolu et al. 2013; Lill et al. 2015), and ALS (Cady et al. 2014; Lill et al. 2015). The TREM2-neurodegenerative diseases risk relationship has been confirmed by other groups in the cases of PD (Feng et al. 2014; Mengel et al. 2016) and ALS (Lattante et al. 2013; Chen et al. 2015). TREM2 expression is also increased in spinal cord samples from ALS patients and SOD1G93A mice (Cady et al. 2014). It is interesting to note that prion infection elevates TREM2 in microglia; however, TREM2 deficiency does not modulate

microglia phenotype (Zhu et al. 2015), and no association between TREM2 variants and prion-CJD has been found (Slattery et al. 2014). Convergent reports have shown that TREM2 is elevated by plaque-associated mononuclear phagocytes in brains of AD model mice (Frank et al. 2008; Melchior et al. 2010; Jay et al. 2015). However, the impact of TREM2 on cerebral amyloidosis is still under debate, with some studies reporting reduced Aβ pathology in 4 month-old TREM2 deficient APP/PS1 mice (Jay et al. 2015), while TREM2 deficiency in 5XFAD mice results in increased Aβ accumulation at 8 months of age but no effect at an earlier age (Wang et al. 2015b; Rivest 2015; Wang et al. 2016b). Just recently, a study reconciled these reports, showing that TREM2 deficiency ameliorates Aβ deposition early but exacerbates it at a later age through reduction of inflammation-related gene expression and decrease of Aβ uptake by mononuclear phagocytes in APP/PS1-21 mice (Jay et al. 2016).

In addition to TLR and TREM2, GWAS studies have identified CD33 as another immune receptor conferring risk for AD (Hollingworth et al. 2011; Naj et al. 2011). CD33 expression is elevated in AD patients' brains (Malik et al. 2013; Walker et al. 2015; Li et al. 2015b), where it is thought to modulate microglial activation and inhibit Aβ clearance (Griciuc et al. 2013; Bradshaw et al. 2013). An interesting study recently showed that the CD33 risk allele (rs3865444C), which is associated with increased CD33 expression, is linked to increased TREM2 surface expression on mononuclear phagocytes. This is intriguing, given that TREM2 mRNA expression is associated with increased Aβ load (Chan et al. 2015). Strong evidence exists for an association between PD risk and increased CD33 expression, and increased CD33 expression on peripheral monocytes is associated with greater disease burden (Chan et al. 2016). Taken together, it seems that innate immunity–once thought to be completely dispensable for evolution of neurodegenerative disorders–is actually at the epicenter of these syndromes.

Microglia also express various receptors for neurotransmitters, including glutamate, GABA, norepinephrine, cannabinoid, and acetylcholine receptors that mediate neuroprotective or neurotoxic effects depending on the particular receptor system (for review see Liu et al. 2016). Certain types of cannabinoid receptors are increased in postmortem tissue from ALS patients and in rat models of PD (Concannon et al. 2015), and overexpression of cannabinoid receptors has a neuroprotective effect in the 6-hydroxydopamine model of PD (Ternianov et al. 2012). Others have shown that cannabinoid agonists protect against nigrostriatal cell loss in the MPTP mouse model of PD (Price et al. 2009) and inhibit Aβ-induced microglial activation *in vitro* and Aβ toxicity *in vivo* (Ramirez et al. 2005). Interestingly, depletion of adrenergic signaling decreases microglial Aβ phagocytic capacity (Heneka et al. 2010), and indirect activation of microglial glutamate receptors by Aβ has been described (Taylor et al. 2002; Taylor et al. 2003). These studies underline the potential role of neurotransmitters as microglial modulators in neurodegenerative diseases.

5. Gliosis, glial dysfunction and the complement pathway

Direct activation of microglia by pathogenic proteins has been reported for fibrillary PrP (Peyrin et al. 1999; Veerhuis et al. 2002; Sisková et al. 2009; Zhu et al. 2015), Aβ (Yu and Ye 2015; Tu et al. 2015), tau (Chen et al. 2016), α-synuclein (Zhang et al. 2005; Béraud et

al. 2011; Fellner et al. 2013) and SOD1 (Roberts et al. 2013; Kinsella et al. 2016). In a terminal mouse model of PrP^{sc} infection, activation of astrocytes and microglia is observed in brain areas showing vacuolization and pathological accumulation of PrP. Activated microglia also present with elevated endocytic and lysosomal activity, accompanied by recruitment of limited numbers of peripheral macrophages (Williams et al. 1994a; Williams et al. 1994b) and $CD4^+$ T cells (Betmouni et al. 1996; Togo et al. 2002; Brochard et al. 2009). Initial microglial activation coincides with changes in neuronal morphology early during the disease process (Williams et al. 1997; Jeffrey et al. 2000)–before neuronal loss and clinical signs (Williams et al. 1997; Giese et al. 1998; Betmouni and Perry 1999). This suggests that injured neurons further exacerbate local glial activation.

With regards to other neurodegenerative diseases, molecular imaging studies have revealed widespread microglial activation in the AD brain (Edison et al. 2008), and clinico-pathological studies support a strong correlation between microglial abundance and disease severity (McGeer et al. 1987; Bornemann et al. 2001; Bolmont et al. 2008; Okello et al. 2009; Arends et al. 2000; Vehmas et al. 2003; Cagnin et al. 2006), suggesting that reactive microglia play a salient role in AD pathogenesis. In terms of PD, patients present with chronic neuroinflammation characterized by focal activation of microglia and astrocytes, and infiltration of lymphocytes (McGeer et al. 1988; Mirza et al. 2000; Imamura et al. 2003; Orr et al. 2005; Brochard et al. 2009; Hirsch and Hunot 2009). It is noteworthy that microglia predominantly segregate near degenerated dopaminergic neurons in PD patient brains (Banati et al. 1998). In ALS, deletion of mutant SOD1 in astrocytes and microglia slows progression of the disease in an ALS mouse model without affecting disease onset (Boillée et al. 2006; Yamanaka et al. 2008), suggesting that reactive glia modify neuronal toxicity induced by mutant SOD1 (Nagai et al. 2007).

A new type of glial cell, namely the aberrant astrocyte-like cell (AbA), has been reported in rodent models of ALS (Trias et al. 2017). AbAs seem to originate from phagocytic microglia and express both astrocytic markers (i.e., GFAP, S100β and Cx43) and microglial markers (such as Iba1 and CD163), but do not express glutamate transporter. Interestingly, their emergence in the degenerating spinal cord is coincident with ALS disease onset in rodent models of the disease (Trias et al. 2017). A few studies have reported peculiar astrocytes populations in ALS patients suggesting that AbAs or a related type of reactive glial cell may also arise in human disease, but this remains to be proven (Trias et al. 2017). There is undoubtedly interest in exploring the role(s) of AbAs and other aberrant glial cell phenotypes in the context of neurodegenerative disease.

Mounting evidence now indicates that microglia become dysfunctional in the ageing brain and during exposure to build-up of misfolded proteins. Recent studies have identified AD risk polymorphisms in a variety of innate immune genes, not only including TREM2 (Guerreiro et al. 2013; Jonsson et al. 2013; Benitez et al. 2014) and CD33 (Griciuc et al. 2013; Bradshaw et al. 2013), but also CLU (which encodes clusterin), PICALM (encoding phosphatidylinositol binding clathrin assembly protein) (Harold et al. 2009) and HLA-DRB5–DRB1 (human leukocyte antigen – antigen D related) (Lambert et al. 2013). A common phenotype linking TREM2 and other innate immune gene risk alleles (*e.g.,* CR1, CD33, MS4A4, MS4A6A, CD2AP, EPHA1) is modulation of microglial phagocytosis.

Interestingly, variants of these genes are also risk factors for other degenerative diseases–*i.e.* TREM2 for ALS (Cady et al. 2014), and HLA-DRB5–DRB1 for PD (International Parkinson Disease Genomics Consortium et al. 2011).

In the context of neurodegenerative diseases, microglia lose their ability to phagocytose Aβ (Hickman et al. 2008; Mawuenyega et al. 2010), α-synuclein (Bliederhaeuser et al. 2016) and infectious prion proteins (Sisková et al. 2009). Interestingly, hyperphosphorylated tau has recently been shown to promote microglial degeneration (Sanchez-Mejias et al. 2016), and also to activate microglia towards increased phagocytosis of insoluble Aβ (Chen et al. 2016). In the mutant SOD1 mouse model of ALS, changes have been reported in microglial molecular signature(s) including loss of P2ry12, Tmem119, Olfml3, transcription factors Egr1, Atf3, Jun, Fos, and Mafb, and the upstream regulators Csf1r, Tgfb1, and Tgfbr1 (Butovsky et al. 2015). This altered microglial phenotype seems to be accompanied by compromised phagocytosis (Butovsky et al. 2015).

Recent reports have shed light on the role of the complement pathway as a regulator of glial phagocytosis in neurodegenerative diseases. The complement cascade is strongly activated in brains of AD patients and rodent models of the disease (Bradt et al., 1998; Tacnet-Delorme et al., 2001; Fan and Tenner, 2004; Sim et al. 2007; Loeffler et al., 2008), and complement receptor 1 has been identified as a genetic risk factor for AD (Lambert et al., 2009; Crehan et al., 2012). Complement cascade components C1q, C3 or C3 receptor regulate microglial synaptic pruning in AD (Hong et al. 2016). Others have shown that astrocyte-derived C3 interacts with microglial C3R to mediate Aβ pathology and neuroinflammation in APP/PS1 model mice (Lian et al. 2016). Additionally, clearance of Aβ from the peripheral circulation is complement-mediated (Brubaker et al. 2017; Crane et al. 2017). Complement pathway activation has also been reported in PD (Yamada et al. 1992; McGeer et al. 2004; Finehout et al. 2005; Wang et al. 2011), and C1q has been implicated in neuromelanin clearance in the PD context (Depboylu et al. 2011); yet, it deserves noting that the contribution of C1q to cognitive impairment is still under debate (Carbutt et al. 2016).

Complement activation has also been found in plaques in PrD patients' brains (Ishii et al. 1984; Nawrocka-Kunecka et al. 2005; Kovacs et al. 2004) and in brain tissue from scrapie-infected rodents (Lv et al. 2015). Additionally, several reports indicate that soluble prion oligomers activate the complement cascade (Dumestre-Perard et al. 2007; Sim et al. 2007), and complement activation occurs early on in the course of prion pathogenesis in rodent models (Klein et al. 2001; Zabel et al. 2007; Michel et al. 2012; Michel et al. 2013). Similarly, high levels of various complement proteins were found in ALS patient CSF and motor endplates (Annunziata et al. 1985; Tsuboi et al. 1994; Bahia El Idrissi et al. 2016) and in rodent models of the disease (Lobsiger et al. 2007, Heurich et al. 2011). While debatable (Lobsiger at al. 2013), it has been proposed that aberrant complement activation in ALS impacts recruitment of macrophages and leads to motor neuron injury (Woodruff et al. 2008, Wang et al. 2017, Lee et al. 2017).

6. On the role of anti-inflammatory mediators

In concert with microglia, activated astrocytes can produce various inflammatory and neurotoxic factors including cytokines and free radicals; triggering a vicious cycle of inflammation that likely exacerbates neurodegeneration (Johnston et al. 2011). Myriad cytokines and chemokines have been detected in brains and CSF of patients suffering from neurodegenerative disorders–leading to the general acceptance that chronic neuroinflammation is a driving force for disease progression (Heneka et al. 2015, Andreasson et al. 2016). Pro-inflammatory mediators have been the center of attention, and their role(s) in neurodegenerative diseases have been extensively reviewed elsewhere (Heneka et al. 2015; Hooten et al. 2015; Alam et al. 2016; López González et al. 2016). However, anti-inflammatory cytokines and other immune suppressive molecules can also be detrimental in neurodegenerative diseases (Weitz and Town 2012; Colangelo et al. 2014; Doty et al. 2014). In this section, we will focus on anti-inflammatory responses that have long been overlooked as culprits in neurodegenerative disorders and are only just recently gaining attention from the scientific community. Two primary examples are the cardinal anti-inflammatory immunosuppressive cytokines, interleukin-10 (IL-10) (Lobo-Silva et al. 2016) and transforming growth factor β (TGF-β) (Zheng et al. 2016), which are elevated in a number of neurodegenerative disorders (see Table 2).

Interestingly, a functional polymorphism within the human *IL10* gene has been associated with risk for late-onset AD in some (but not all) populations (Lio et al. 2003; Depboylu et al. 2003; Scassellati et al. 2004; Arosio et al. 2004; Ma et al. 2005; Ramos et al. 2006; Vural et al. 2009). Strikingly, all elements of the IL-10 signaling pathway are abnormally elevated in AD patients' sera and brains and in rodent models of the disease (Angelopoulos et al. 2008; Loewenbrueck et al. 2010; Gezen-Ak et al. 2013; Asselineau et al. 2015; Guillot-Sestier et al. 2015a; Guillot-Sestier et al. 2015b), and recent GWAS/integrative genomics studies validate these findings (Zhang et al. 2013; Li et al. 2015a). Aged microglia have elevated expression of IL-10/STAT3 pathway genes (Sierra et al. 2007; Henry et al. 2009; Kingery et al. 2013), and IL-10 abundance is increased in plasma and in reactive glia surrounding amyloid-β plaques in aged mouse models of AD (Apelt and Schliebs 2001; Guillot-Sestier et al. 2015a). We and others studied the effects of the IL-10 pathway on cerebral amyloidosis using animal models. On one hand, *Il10* genetic ablation in APP/PS1 mice activates mononuclear phagocytes to clear cerebral amyloid, without coming at the cost of bystander neuronal injury (Guillot-Sestier et al. 2015a). Indeed, synaptic integrity and cognitive deficits are rescued in APP/PS1/IL-$10^{-/-}$ mice compared to APP/PS1/IL-$10^{+/+}$ controls (Guillot-Sestier et al. 2015a). In complementary fashion, cerebral *Il10* overexpression using adeno-associated virus in TgCRND8 and Tg2576 mice exacerbates Aβ plaque number and size and decreases synaptic protein abundance; worsening cognitive impairment (Chakrabarty et al. 2015).

Several studies have explored the risk relationship between neurodegenerative diseases and the IL-10 pathway. Similar to the case of human AD, polymorphisms within *IL10* that affect levels of cytokine production correlates with PD in some but not all populations (Bialecka et al. 2007; Infante et al. 2008; Bialecka et al. 2008; Pascale et al. 2011; Iyer and Cheng 2012; Li et al. 2012; Nie et al. 2013; Jin et al. 2014). Interestingly, the G1082A polymorphism in

the *IL10* promoter that correlates with high IL-10 production is related to the age of PD onset (Håkansson et al. 2005), and IL-10 is elevated in PD patient sera (Brodacki et al. 2008; Rentzos et al. 2009). Remarkably, infusion of IL-10 into the substancia nigra of rats protects against LPS-induced cell death of dopaminergic neurons (Arimoto et al. 2007). In a similar manner, administration of cDNA coding for human *IL10* into the striatum of PD animal models seems to play a protective role on the nigrostriatal dopaminergic system in (6-OHDA) rats (Johnston et al. 2008) and MPTP-treated mice (Joniec-Maciejak et al. 2014). In ALS patients' spinal cords, IL-10RA expression is elevated, and IL-10 immunoreactivity is associated with TDP-43 inclusions in motor neurons (Berjaoui et al. 2015). Further, in a mouse model of ALS, glial cells overexpress IL-10 in presymptomatic disease (Gravel et al. 2016). In this model, blocking *Il10* increases inflammation and exacerbates, while overexpression of *Il10* delays disease onset (Gravel et al. 2016). However, it is not known if the protective role of IL-10 in PD/ALS animal models is durable, and whether it may repress beneficial microglial responses at later disease stages. Interestingly, CNS and CSF IL-10 expression is also increased in another neurodegenerative disorder: Creutzfeldt-Jakob disease (Stoeck et al. 2005).

Second only to IL-10, TGF-β is the other major anti-inflammatory, immunosuppressive cytokine in the body (Li et al. 2008). Release of TGF-β by microglia, astrocytes and oligodendroglia is elevated in response to CNS injury (Constam et al. 1992; Finch et al. 1993), and TGF-β1 levels are increased in AD patients' CSF and serum (Chao et al. 1994b; Chao et al. 1994a). TGF-βR1 immunoreactivity is associated with amyloid-β plaques (van der Wal et al. 1993), and is elevated in AD patient reactive microglia vs. controls (Lippa et al. 1998). In TgCRND8 transgenic mouse model of AD, brain TGF-β1 is elevated, where it amplifies Aβ-induced neurodegeneration (Salins et al. 2008). This suggests that the AD brain may try to over-compensate for Aβ insult by inappropriately producing high levels of TGF-β1 (Wyss-Coray et al. 1997; Wyss-Coray and Mucke 2002), thereby inducing non-productive low-level neuroinflammation that impairs amyloid-β clearance. Moreover, this "cloud" of brain TGF-β1 acts as an inhibitory signal to keep peripheral innate cells with Aβ clearance aptitude out of the CNS. In support of this, our group has previously demonstrated that genetic blockade of peripheral TGF-β-Smad 2/3 signaling in the Tg2576 transgenic mouse model of cerebral amyloidosis promotes mononuclear phagocyte homing to the CNS and resolution of Aβ deposits (Town et al. 2008; Town 2009; Rezai-Zadeh et al. 2009; Town 2010; Gate et al. 2010). Interestingly, when overexpressing TGF-β1 under the GFAP promoter in hAPP transgenic mice, others reported promotion of microgliosis and repartitioning of Aβ deposits from brain parenchyma to cerebral vessels in transgenic mice overexpressing $hAPP_{V717F}$ (Wyss-Coray et al. 1997; Wyss-Coray et al. 2000; Wyss-Coray et al. 2001). Interestingly, TGF-β1 stimulated cultured microglial cells to clear synthetic Aβ, suggesting that the *in vivo* effect of astrocyte TGF-β1 overexpression might be mediated by activated microglia (Wyss-Coray et al. 2001). In another study, reduced neuronal TGF-β signaling in hAPP mice increased amyloid-β load and neurodegeneration *in vivo* (Tesseur et al. 2006), likely due to neuronal cell-autonomous effects of TGF-β removal. These apparent discordancies highlight the exquisite cell-dependent contextual effects of TGF-β, and that TGF-β-driven responses often follow a U-curve pattern.

In the context of PD, TGF-β1 levels are elevated in patient striatum and CSF samples (Mogi et al. 1995; Vawter et al. 1996; Nagatsu et al. 2000), and mice bilaterally infused into the Substantia Nigra with α-synuclein have increased TGF-β striatal mRNA levels (Sznejder-Pacholek et al. 2016). Importantly, TGF-β1 is known to be neuroprotective and neurotrophic for dopaminergic neurons (Krieglstein et al. 1995; Unsicker et al. 1996; Knöferle et al. 2010). In Parkinsonian rats, TGF-β1-releasing extra-adrenal chromaffin cell grafts have shown functional benefit in terms of regeneration (Espejo et al. 2001; Fernandez-Espejo et al. 2005; Galan-Rodriguez et al. 2008), and in the same rodent model, TGF-β1 potentiates GDNF-mediated dopamine trophic effects (Gonzalez-Aparicio et al. 2010). Strikingly, inhibition of TGF-β signaling worsened Parkinsonism in mice given MPTP, while increasing TGF-β signaling reduced Parkinson disease-related pathologies and motor deficits (Tesseur et al. 2017). Similarly, TGF-β1 is increased in plasma and CSF of ALS patients and positively correlates with disease stage and duration (Houi et al. 2002; Iłzecka et al. 2002; Iwasaki et al. 2003). In addition, phosphorylation of the proximal TGF-β downstream effector, Smad2/3, is increased in neuronal and glial nuclei of sporadic and familial ALS patients and in mutant human SOD1 transgenics (Nakamura et al. 2008). *In vitro* activation of TGF-β/Smad 2/3 signaling reduces aggregate formation of cytoplasmic mis-localized TDP-43 (Nakamura et al. 2013), and bioinformatics has identified modulation of TGF-β signaling pathway as a contributor to motor neuron degeneration in ALS (Phatnani et al. 2013). Increased expression of miR-155 in mSOD1 mice–mimicking increased miR-155 found in the spinal cords of both familial and sporadic ALS–is accompanied by loss of TGF-β1 and TGF-βR1 expression amongst changes in other innate immune molecules. At least in this context then, phagocytic capacity is suppressed. Conversely, genetic ablation of miR-155 in mutant human SOD1 transgenic mice restores abnormal microglial phenotype and endorses beneficial functions (Butovsky et al. 2015). Other reports show that astrocyte-derived TGF-β1 disrupts the neuroprotective function of microglia and accelerates ALS progression in SOD1 mice (Endo et al. 2015). Furthermore, pharmacological inhibition of TGF-β signaling extends survival of SOD1 transgenics (Endo et al. 2015), indicating that overabundance of astrocytic TGF-β is detrimental in the ALS context (Endo and Yamanaka 2015). Interestingly, TGF-β1 mRNA and protein levels were enhanced in the ME7 murine model of prion disease (Betmouni et al. 1999), suggesting TGF-β1 pathway activation in the context of prionopathy (Cunningham et al. 2002). More specifically, this early report suggests that TGF-β1 controls microglial phenotype in the context of prion diseases. Indeed, a more recent ME7 mouse gene screening strategy placed TGF-β as a key factor promoting the microglial pro-neurogenic response during chronic neurodegeneration (De Lucia et al. 2016).

Targeting production of cytokines themselves could also be of therapeutic value. Endogenous over-production of anti-inflammatory cytokines (*e.g.*, IL-10 and TGF-β) is likely reflective of an attempt to protect neurons from inflammatory bystander damage. But timing is everything. During early stages of neurodegenerative disease, this response is likely beneficial. However, as the disease becomes chronic, immunosuppression proves to be maladaptive. Mounting evidence shows that chronic dysregulation of immune homeostasis is deleterious. For example, we and others showed that inhibiting IL-10/STAT3 signaling dramatically mitigates Alzheimer-like pathology (Guillot-Sestier et al. 2015a), while brain

overexpression of *Il10* produces complementary effects (Chakrabarty et al. 2015; Michaud and Rivest 2015). Blockade of TGF-β-Smad 2/3 signaling in peripheral macrophages causes brain infiltration of these cells and mitigation of cerebral β-amyloidosis (Town et al. 2008). Likewise, elevation of TGF-β is deleterious in ALS (Endo et al. 2015; Endo and Yamanaka 2015), and others have shown that microglia can be rebalanced to ameliorate pathology in a transgenic ALS mouse model (Gravel et al. 2016; Wang et al. 2016a). Interestingly, reduced inflammation in aged APP/PS1-TREM2 deficient mice is associated with reduced amyloid-β clearance (Jay et al. 2016).

7. Conclusions

It is now becoming clear that broad-based anti-inflammatory therapeutics (*i.e.*, non-steroidal anti-inflammatory drugs) will ultimately not be the best way forward as an AD treatment (Szekely and Zandi 2010; Miguel-Álvarez et al. 2015). These negative findings have raised awareness to the ironic notion that blocking immunosuppressive pathways may actually be beneficial as a therapeutic approach for neurodegenerative diseases that share common denominators, such as neurotoxic misfolded proteins. Rewiring the cerebral innate immune response by inhibiting actions of key anti-inflammatory cytokines could allow the brain to return to a physiological state, and may therefore represent a therapeutic approach (Figure 1).

The literature detailed in this review demonstrates that neuroinflammation is not always damaging; in principle, innate immunity could actually be harnessed to treat neurodegenerative diseases. Specifically targeting the beneficial responses and dampening detrimental neuroinflammation has become the critical question in neurodegenerative disease research. Another important question is when to therapeutically intervene–at early or late clinical stages. With respect to modeling microglial phenotypes in the dish, it is particularly important to keep in mind that microglia obtained from rodent neonates have a macrophage-like profile that may not represent human adult or senescent microglial physiology. Finally, specifically targeting recruitment of blood-borne monocytes to promote phagocytosis of misfolded proteins is an area that is garnering intense interest (Wisniewski et al. 1991; Gate et al. 2010; Depboylu et al. 2012; Weitz and Town 2016; Prinz and Priller 2017). Embedded within this last question is the need to better understand the relative contribution of CNS vs peripheral mononuclear phagocytes to neurodegenerative diseases.

With an eye toward future research, an emerging area is the contribution of the gut microbiome to neurodegenerative diseases. While it’s early days yet, a broader understanding of how gut commensals contribute to evolution of AD and PD is becoming increasingly important (for review, see Ghaisas et al 2016; Sherwin et al. 2017). Indeed, through the so-called gut-brain axis, the gastrointestinal tract communicates with the CNS to support or destabilize neuronal health. Defining the role(s) of the innate immune system in gut-brain communication may lead to new strategies to alter gut microbiota populations in order to manage neurodegenerative diseases.

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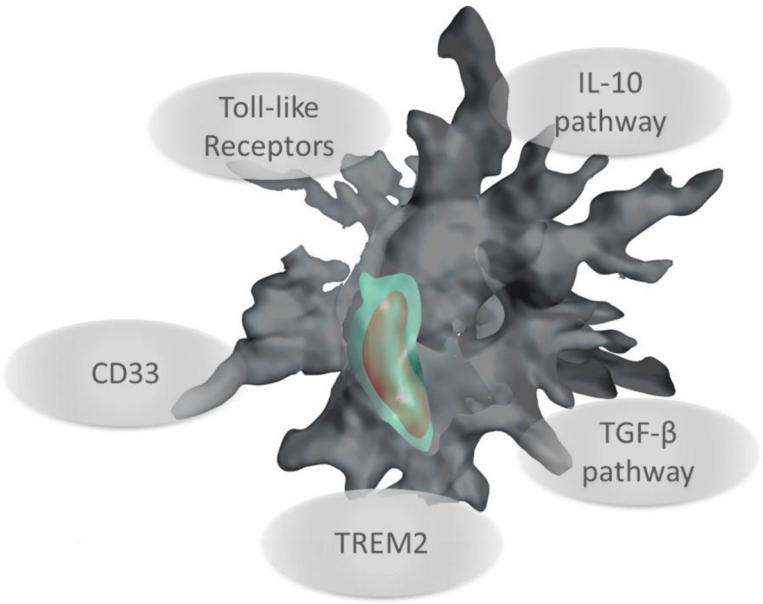

Figure 1.

Targeting innate immune receptors and anti-inflammatory pathways to promote innate immunity against neurodegenerative diseases. The cartoon depicts a mononuclear phagocyte (gray) engulfing abnormal proteins (red) into a phagolysosome (green).

Table 1

Summary of proteinopathies associated with the most common neurodegenerative diseases

Pathology	Nature of abnormal protein aggregate	CNS regions most affected	Exosomal transport
Alzheimer's Disease (AD)	Amyloid-β (Aβ) hyper phosphorylated Tau	Hippocampus Cortex Basal forebrain Brain stem	YES
Amyotrophic Lateral Sclerosis (ALS)	Superoxide dismutase 1 (SOD1) TAR DNA-binding protein 43 (TDP43) Dipeptide repeat protein (DPR)	Motor Cortex Spinal motor neurons	YES
Parkinson's Disease (PD)	α-synuclein	Substancia Nigra Cortex Locus Coeruleus Raphe	YES
Prion diseases (PrD)	Prion protein scrapie (PrP^{sc})	Cortex Thalamus Brain stem Cerebellum	YES

Table 2

Roles of anti-inflammatory mediators in neurodegenerative disorders

	IL-10 pathway		**Experimental Effects**	
	Human	**Rodent**	**Overexpression**	**Blockade/deletion**
AD	• Functional polymorphism in certain populations • Signaling pathway elevated in brain • Levels increased in sera	• Signaling pathway elevated in brain • Levels increased in sera • Elevated in plasma and in reactive glia associated with Aβ plaques	• Suppresses microglial Aβ phagocytosis *in vitro* • Increases Aβ accumulation • Exacerbates synaptic loss and memory impairment	• Increases microglial Aβ phagocytosis *in vitro* and *in vivo* • Activates cerebral Aβ clearance • Rebalances innate immunity • Rescues synaptic integrity and cognitive deficits
ALS	• IL10-RA expression is elevated in spinal cord • IL-10 expression is associated with TDP-43 inclusions in motor neurons	• Overexpressed in glial cells in a mouse model of ALS	• Delays disease onset	• Exacerbates disease • Increases inflammation
PD	• Polymorphism in certain populations • High IL-10 production correlates with disease onset • Elevated in sera	*Not Reported*	• Protects against LPS-induced death of dopaminergic neurons • Protective in 6-OHDA rats and MPTP-treated mice	*Not Reported*
PrD	• CSF and CNS expression increased in Creutzfeldt–Jakob disease	• No differences observed	*Not Reported*	*Not Reported*
	TGF-β pathway		Experimental Effects	
	Human	Rodent	Overexpression	Blockade/deletion
AD	• TGF-β1 is increased in CSF and sera • TGF-βR1 immunoreactivity is associated with Aβ plaques • TGF-βR1 is increased in reactive microglia	• Increased TGF- β1 brain expression in transgenic AD mouse models	• TGF- β1 overexpression in astrocytes promotes microgliosis and Aβ deposition in cerebral vessels • Increased microgliosis and reduced parenchymal Aβ load in hAPP/TGF-β1 bigenic mice	• Blockade of TGF-β-Smad 2/3 signaling in peripheral mononuclear phagocytes in Tg2576 mice resolves Aβ deposits and mitigates cognitive impairment • Inhibiting neuronal TGF-β signaling increases Aβ load and promotes neurodegeneration
ALS	• TGF-β1 is elevated in plasma and CSF	• Increased phosphorylation of	• Astrocyte derived TGF-β1 accelerates ALS progression in	• Loss of TGF-β1 andTGF-βR1 expression induced by

	IL-10 pathway		**Experimental Effects**	
	Human	**Rodent**	**Overexpression**	**Blockade/deletion**
	• TGF-β1 expression positively correlates with disease stage and duration • Increased phosphorylation of Smad2/3 in neuronal and glial nuclei	Smad2/3 in human SOD1 transgenic mice	SOD1 transgenic mice	increased expression of miR-155 in mSOD1 mice leads to reduced phagocytosis • Pharmacological inhibition of TGF-β signaling extends survival of SOD1 transgenic mice
PD	• TGF-β1 levels are elevated in striatum and CSF	• Injection of α-synuclein into the Substancia Nigra increases striatal TGF-β1 mRNA levels	• TGF-β1-releasing chromaffin cell grafts are beneficial in Parkinsonian rats • TGF-β1 potentiates GDNF-mediated trophic effects in a PD rat model • Reduced disease in MPTP-injected mice	• Enhanced PD-related pathology and motor deficits in MPTP-injected mice
PrD	*Not Reported*	• TGF-β1 mRNA and protein levels are enhanced in the ME7 mouse model of scrapie	• TGF-β1 signaling controls the microglial pro-neurogenic response	*Not Reported*