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Inflammation in the early stages of neurodegenerative pathology

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Abstract

Inflammation is secondary to protein accumulation in neurodegenerative diseases, including Alzheimer's, Parkinson's and Amyotrophic Lateral Sclerosis. Emerging evidence indicate sustained inflammatory responses, involving microglia and astrocytes in animal models of neurodegeneration. It is unknown whether inflammation is beneficial or detrimental to disease progression and how inflammatory responses are induced within the CNS. Persistence of an inflammatory stimulus or failure to resolve sustained inflammation can result in pathology, thus, mechanisms that counteract inflammation are indispensable. Here we review studies on inflammation mediated by innate and adaptive immunity in the early stages of neurodegeneration and highlight important areas for future investigation.

Keywords

neuro-inflammation; neurodegeneration; fractlakine; TRAIL

Introduction

The immune system is essential for the maintenance of tissue homeostasis and the response to infection and injury. Microglia, a type of glial cells, are macrophages that are resident in the central nervous system (CNS) and the major resident immune cells in the brain, where they provide innate immunity (Ransohoff and Perry, 2009). In normal brains, microglia show ramified, highly motile processes undergoing cycles of protrusion, extension, and withdrawal allowing them to monitor the local microenvironment and detect CNS damage (Nimmerjahn et al., 2005). Microglia release factors that influence another type of support glial cells, called astrocytes, as well as neurons. Under physiological conditions, microglia are deactivated and they provide innate immunity, producing anti-inflammatory and neurotrophic factors (Streit, 2002). Under stress, including pathogen invasion, injury or abnormal protein accumulation, microglia provide adaptive immune responses, become activated and thereby promote an inflammatory response to stimulate the immune system and eradicate the stress stimulus. In some cases, the microglia inflammatory response is self-controlled, resolving once the stress stimulus is terminated. Innate inflammation is reported

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in Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS) and a number of other nervous system pathologies (reviewed in (Akiyama et al., 2000).

Inflammatory stimuli may induce beneficial effects such as phagocytosis of debris and apoptotic cells and initiate repair processes, but uncontrolled inflammation can result in production of neurotoxic factors that exacerbate neurodegenerative pathology. The inflammatory response involves a delicate balance between the innate and adaptive immune systems to deal with inflammatory stimuli. As a consequence, genes that are critical to amplification of inflammatory responses are normally repressed under physiological conditions and are only induced when cells are stressed. Inflammatory responses are initiated by pattern recognition receptors, which include the Toll-like receptors (TLRs) that recognize “invading” pathogen-associated molecules (Takeuchi and Akira, 2010). For example, TLR4 recognizes lipopolysaccharide (LPS) associated with gram-negative bacteria, and TLR3 recognizes viral double-stranded RNA. TLRs are highly expressed on macrophages and microglia and may respond to endogenously derived molecules, such as protein aggregates or signals released from apoptotic cells. TLR2 and TLR4 are implicated in chronic inflammation in animal models, and specific TLR4 polymorphisms are associated with several human diseases, including atherosclerosis, type 2 diabetes, and rheumatoid arthritis, raising the possibility of involvement of these receptors in neurodegeneration (Balistreri et al., 2009). In addition to TLRs, purinergic receptors (e.g., P2×7) are also expressed on microglia and astrocytes and can respond to ATP released from apoptotic cells (Di Virgilio et al., 2009). Microglia and astrocytes respond to cell signaling via so-called “scavenger receptors” that are involved in the phagocytosis of oxidized proteins, lipids, and apoptotic cells (Husemann et al., 2002).

Inflammatory responses are typically localized and involve communication between immune and other CNS cells. CNS resident microglia exhibit a deactivated phenotype (ramified) in the healthy brain and maintain tissue homeostasis through communication with astrocytes and neurons (Lumeng et al., 2007). The phenotype of resident macrophages is considered activated and designated M1 or “classical activation”, which describes the pro-inflammatory phenotypic response. M2 or “alternative activation” describes phenotypic responses to cytokines, such as interleukin (IL)-4 and IL-13 (Nathan and Ding, 2010). Therefore, transition of macrophages from the M1 to the M2 phenotype is generally indicative of inflammatory pathology. The CNS is an immunologically privileged site and circulating immune cells normally do not have access to it in the absence of inflammation or injury. Dendritic cells with specialized antigen-presenting capabilities are not present under normal conditions, but when microglia sense danger through TLR4, they secrete inflammatory mediators such as tumor necrosis factor (TNF)-α and IL-1β to act on astrocytes and induce secondary inflammatory responses (Saijo et al., 2009). The initiation of an immune response involves the development of adaptive immunity. Inflammatory markers include cytokines (e.g., TNF-α, IL-1β) that amplify inflammation; and chemokines like monocyte chemotactic protein-1 (MCP-1) that recruit additional immune cells. In addition, inflammation induces genes that encode proteins with antimicrobial activities such as inducible nitric oxide synthase (iNOS) and genes that modulate substrate metabolism, protein synthesis, cell motility, phagocytosis, and antigen presentation. However, inflammatory responses may induce collateral damage such as the generation of reactive oxygen species (ROS). Furthermore, induction of proteins that inhibit signal transduction pathways such as suppressor of cytokine signaling (SOCS) proteins, transcriptional repressors like activating transcription factor-3 (ATF3), Nuclear receptor related protein-1 (Nurr1), anti-inflammatory molecules (e.g. IL-10), transforming growth factor beta-1 (TGF-β) and ligands for TAM (Tyro3, Axl and Mer) receptors are mechanisms that may resolve inflammation.

Alzheimer's disease and β-amyloid

AD is an aging disorder, characterized by extracellular deposits known as senile plaques, which consist of aggregates of amyloid-p (Aβ) peptide (Glenner and Wong, 1984; Masters et al., 1985). Proteolytic cleavage of amyloid precursor protein (APP) by the β-site APP cleaving enzyme (BACE1) near the C-terminus results in the formation of APP C-terminal fragment (CTFβ) C99. Subsequent cleavage of CTFβ by γ-secretase generates Aβ of 40 ($A\beta_{40}$) or 42 ($A\beta_{42}$) residues (Jarrett et al., 1993). Alternatively, APP cleavage by α-secretase to generate APP (CTFα) C83 occurs within the Aβ region, precluding its formation (Allinson et al., 2003; Li et al., 1999). Plaques containing the N-terminal APP cleavage products $A\beta_{42}$ and/or $A\beta_{40}$ are the hallmarks of AD pathology (Haass and Selkoe, 2007). Rare mutations in APP and the presenilin (PS) components of γ-secretase are causes of familial AD, providing one line of evidence that Aβ contributes to the pathogenesis of AD (Bertram and Tanzi, 2008). Intracellular accumulation of Aβ in transgenic animals and brains of human patients with AD and Down's syndrome (von Kienlin et al., 2005) provide evidence for the presence of intracellular Aβ within neurons. $A\beta_{42}$ is found in multivesicular bodies (MVBs) of neurons in the human brain, where it is associated with synaptic pathology (Takahashi et al., 2002). In triple transgenic AD (3xTg-AD) mice, which overexpress APP_{Swe}, Tau_{P301L} and harbor $PS1_{M146V}$ knock-in mutation, soluble and oligomeric Aβ accumulate within neuronal cell bodies, but the intraneuronal pool decreases when extracellular plaques appear (Oddo et al., 2006), consistent with data from human brain tissue (Gyure et al., 2001; Mori et al., 2002; Ohyagi et al., 2007). Taken together, these data suggest that in early stage AD, the human brain might have abundant intraneuronal Aβ, which then becomes extracellular as the disease progresses and neurons die. The presence of an intraneuronal pool of Aβ suggests that AD pathology may have an intraneuronal or pre-plaque stage. We have previously demonstrated that intraneuronal Aβ triggers AD-like pathology, including inflammation in gene transfer animal models without detection of extracellular plaque (Burns et al., 2009; Rebeck et al., 2010).

Evidence of an inflammatory response in AD is manifest in change of microglia morphology from ramified (deactivated) to amoeboid (activated), as well as astrogliosis surrounding plaques. Microglia surrounding plaques stain positive for activation markers and pro-inflammatory mediators, including major immuno-histocompatibility complex (MHC)-II, cyclooxygenase (Cox)-2, MCP-1, TNF-α, IL-1β, and IL-6 (Akiyama et al., 2000). MCP-1 is known to induce the chemotaxis of astrocytes and contribute to the recruitment of astrocytes around plaques (Wyss-Coray et al., 2003). In addition, elevated levels of chemokines and cytokines and their receptors, including IL-1α, CXCR2, CCR3, CCR5, and TGF-β, have been reported in post-mortem AD brains (Cartier et al., 2005). Furthermore, we demonstrated that pre-plaque Aβ activates microglia and astrocytes and increases inflammatory markers in gene transfer animal models 4 weeks post-injection (Rebeck et al., 2010), suggesting that inflammation in AD may not only be a response to extracellular plaque build-up, but involves communication between Aβ-expressing neurons and microglia. Additionally, intraneuronal accumulation of Aβ can cause cell death and apoptosis, triggering neuronal signals to activate microglia and astrocytes (Pereira et al., 2005), independent of extracellular Aβ deposition. Aggregates of Aβ can activate microglia and induce factors such as NO, ROS, pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6), chemokines (e.g., IL-18), and prostaglandins (e.g., PGE2), that promote neuronal death (Akiyama et al., 2000; Kitazawa et al., 2004).

Microglia and astrocytes can detect Aβ through a number of sensors, including TLRs, that are expressed on glial cells (Landreth and Reed-Geaghan, 2009). In particular, Aβ may activate microglia and astrocytes through TLR4 (together with CD14 and MD2 in microglia) (Reed-Geaghan et al., 2009; Walter et al., 2007). Mice carrying a non-functional TLR4

crossed with APP/PS1 double transgenic mice produce fewer inflammatory cytokines (Jin et al., 2008). It has been suggested that TLR4 may participate in the phagocytosis of Aβ plaques by microglia. Indeed, mice carrying mutant TLR4 crossed with AD transgenic mice exhibit more Aβ plaques (Tahara et al., 2006). However, microglia response to intraneuronal or pre-plaque Aβ is still poorly understood, and may reflect the early stages of disease pathogenesis. Intracellular accumulation of Aβ may lead to fibrilization and apoptotic death. Aβ fibrils are suggested to trigger inflammatory responses through TLR4/TLR6 in the presence of CD36 (Stewart et al., 2010). TLR9 stimulation by CpG-DNA (a mimic of bacterial DNA) shows neuroprotective roles both *in vivo* and *in vitro* (Doi et al., 2009). TLR2 may also be a sensor for fibrillar Aβ. Mice lacking TLR2 crossed with APP/PS1 transgenic AD mice show delay in Aβ deposition and ameliorated behavioral performance (Richard et al., 2008). The action of TLRs may mediate neuronal-glial signaling in pre-plaque models of AD, mimicking mild cognitive impairment (MCI), and possibly leading to inflammatory responses that are distinctively different from microglia activation in the presence of plaques. Intraneuronal accumulation of Aβ alters several cellular processes, including mitochondrial integrity and endoplasmic reticulum, leading to apoptotic cell death. NOD-like receptors (NLRs) sense cellular damage and cytoplasmic pattern recognition receptors for pathogens (Reviewed (Schroder and Tschopp, 2010; Schroder et al., 2010). In AD, Aβ oligomers and fibrils induce lysosomal damage and trigger NALP3, a member of the NLR family that is expressed on microglia (Halle et al., 2008). We recently showed that intraneuronal Aβ can disrupt autophagic clearance and result in autophagosome accumulation (Khandelwal et al., 2011), so it will be interesting to examine the mechanisms of microglia response to neurons undergoing autophagy. Accumulation of intraneuronal Aβ may induce lysosomal and MVBs damage leading to leakage of Aβ from vesicles into the cytosol and activation of inflammatory mechanisms, without extracellular build-up of amyloid plaques. Additionally, macrophages may be differentially activated in pre-plaque inflammation due to lack of extracellular deposits.

It is worth mentioning that divergent results have been obtained in attempts to assess the overall impact of microglia on AD pathology in mice. In one approach, APP/PS1 transgenic AD mice were crossed to mice in which microglia, but not macrophages, could be conditionally depleted. Three weeks after conditional depletion of microglia, amyloid plaque formation and neuronal damage did not change in comparison with control mice (Grathwohl et al., 2009). Paradoxically, recent experiments in which the growth factor macrophage colony-stimulating factor **(**M-CSF or CSF-1) was systemically administered to APP/PS1 transgenic mice for 4 months, resulted in a significant increase in the number of parenchymal microglia, decreased Aβ deposits, and decreased cognitive loss (Boissonneault et al., 2009), thereby supporting a neuroprotective function.

Advanced glycoxidation end-products (RAGE) is a cell surface receptor belonging to the immunoglobulin superfamily and provides an Aβ sensor (Neeper et al., 1992; Schmidt et al., 1992). Aβ peptides as well as Aβ oligomers bind to RAGE and microglia (Yan et al., 1996). Blocking the interaction of Aβ with RAGE impairs the activation of microglia and reduces the production of pro-inflammatory mediators (Ramasamy et al., 2009). RAGE is also suggested to play an important role in the clearance of Aβ and to be involved in apolipoprotein E (ApoE)-mediated cellular processing and signaling (Bu, 2009). ApoE is a transporter of lipids and in humans has three isoforms: apoE2, apoE3, and apoE4. The apoE4 allele is associated with an increased risk of AD (Bu, 2009). Since ApoE is expressed in glial cells, studies are needed to better understand the role of microglia in response to variations in ApoE allele expression, which suggest that the ApoE4 allele may compromise microglia ability to clear Aβ.

Tau in parkinsonism and dementia

In addition to Aβ, Tau is another causal factor for neurodegeneration in primary Tauopathies, including AD, fronto-temporal dementia with parkinsonism linked to chromosome 17 (FTDP-17), cortical basal degeneration (CBD) and progressive supranuclear palsy (PSP) (Buee et al., 2000; Dawson and Dawson, 2003; Di Maria et al., 2000; Dickson, 1999; Lippa et al., 2005; Pletnikova et al., 2005; Popescu et al., 2004; Yancopoulou et al., 2005). Tau comprises a family of six proteins from a single gene by alternative mRNA splicing (Goedert et al., 1989; Himmler et al., 1989). In AD, all six isoforms are hyper-phosphorylated in paired helical filaments (PHFs), which form neurofibrillary tangles (NFTs) (Grundke-Iqbal et al., 1989; Grundke-Iqbal et al., 1986). Hyper-phosphorylation of Tau precedes the appearance of NFTs (Bancher et al., 1989; Kopke et al., 1993), and deposition of $A\beta_{42}$ initiates the molecular mechanism in AD (Younkin, 1995) and gene transfer models (Rebeck et al., 2010). NFTs regulate cytoskeletal changes under normal physiological conditions. An inflammatory environment might activate Tau kinases to promote formation of NFTs (Ballatore et al., 2007), but whether hyper-phosphorylated Tau and NFTs affect inflammatory responses is not yet well understood. We demonstrated in gene transfer animal models expressing wild type and mutant Tau_P301L that increased levels of hyper-phosphorylated Tau are associated with increased inflammatory markers, including TNFα, IL-6, iNOS and activated microglia 4 weeks post injection (Khandelwal et al., submitted). Increasing evidence suggest that neuroinflammation is a common feature of Tauopathies. First, activated microglia are found in the postmortem brain tissues of various human Tauopathies including AD, FTDP, PSP and CBD (Gebicke-Haerter, 2001; Gerhard et al., 2006; Ishizawa and Dickson, 2001). Second, induction of systemic inflammation by LPS via TLR4 significantly induces Tau hyper-phosphorylation in 3xTg-AD mice (Kitazawa et al., 2004). Third, the immunosuppressant drug FK506 attenuates microglia activation and extends the life span of Tau_{P301S} transgenic mouse model of FTDP (Yoshiyama et al., 2007). Finally, pro-inflammatory cytokines, including IL-1, IL-6, and NO are released from astrocytes and can accelerate Tau pathology and formation of NFTs *in vitro* (Li et al., 2003; Quintanilla et al., 2004; Saez et al., 2004). Taken together, these findings suggest a link between neuroinflammation and Tauopathies leading to microglia over-activation and a pathogenic role in the formation of neurodegenerative pathologies. Microglia activation may be a beneficial response leading to clearance of Aβ-loaded cells or may result in exacerbation of neurodegenerative pathology and Tau hyper-phosphorylation.

Aβ formation and associated Tauopathy may explain a cell-autonomous stress response in neurons, as suggested by studies of the N-APP/DR6 mouse model of AD (Nikolaev et al., 2009). Aβ aggregates and products derived from dead cells can trigger microglia and astrocytes through the TLR and RAGE-dependent pathways, leading to local inflammation that may further amplify neuronal death. Pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6, might act directly on neurons to induce apoptosis (McCoy and Tansey, 2008; Simi et al., 2007). Furthermore, TNF-α and IL-1β released by microglia can activate astrocytes, whereas factors released from astrocytes may lead to further activation of microglia (Saijo et al., 2009). In addition, APP, PS and BACE1 have nuclear factor kappa-light-chain-enhancer of activated B cells ($_{NF}$-$_{K B}$) sites in their promoters, and pro-inflammatory cytokines are known to up-regulate their expression in neurons (Sastre et al., 2008). Inflammatory mediators acting on neurons might contribute to more production of Aβ, further activating microglia-mediated inflammation. Therefore, communication between neurons and glia may amplify the production of neurotoxic factors that contribute to neurodegeneration. Region-specific effects on neurons are likely to depend on the specific types of receptors expressed within different neuronal populations. For example, TNF-α mediates the activation of cell survival pathways through $_{NF}$-$_{K B}$ as well as apoptotic signaling pathways through activation

of caspases. Although symptoms of AD are caused by neuronal damage, it is not well understood which neurons are the primary targets of the neurotoxic process. Death of cholinergic neurons in the basal forebrain is an indicator of AD pathology, however, other neurons, such as glutaminergic and GABAergic neurons, are also important targets in AD pathology (Rissman et al., 2007; Yamin, 2009).

Parkinson's disease and α–Synucleinopathies

PD is predominantly sporadic, but some disease-causing mutations suggest a genetic component in the pathogenesis of this disorder. As is the case for AD, rare mutations in a number of genes cause familial forms of PD and provide insights into general pathogenic mechanisms (Gasser, 2009). Mutations in autosomal recessively inherited genes like parkin, PTEN-induced kinase-1 (PINK1) and DJ-1, lead to early onset parkinsonism (Cookson and Bandmann, 2010). Dominantly inherited mutations in leucine-rich repeat kinase 2 (LRRK2) and α-Synuclein cause late onset PD. Genome-wide association studies suggest that naturally occurring sequence variants in α-Synuclein and LRRK2, as well as Tau, constitute an increased risk for late onset sporadic PD (Cookson and Bandmann, 2010; Healy et al., 2004; Martin et al., 2001). PD is characterized by death of dopaminergic neurons in the substantia nigra (SN) (Benner et al., 2008; Kuhn et al., 2006; Reynolds et al., 2008) and formation of inclusions known as Lewy bodies (LBs) (Goedert, 1999; Goedert, 2001; Lundvig et al., 2005; Spillantini et al., 1998a; Spillantini et al., 1998b; Spillantini and Goedert, 2000; Spillantini et al., 1997; Takeda et al., 2000; Trojanowski and Lee, 2003; Wakabayashi et al., 1997). LBs, which primarily contain aggregated α-Synuclein, are pathological markers of a group of diseases collectively known as "Synucleinopathies" (Goedert, 1999; Spillantini et al., 1998a; Spillantini et al., 1998b; Spillantini and Goedert, 2000; Takeda et al., 2000; Wakabayashi et al., 1997). Although idiopathic PD is not associated with NFTs, Tau expression is observed in a sub-population of LBs (Ishizawa et al., 2003). Inclusions formed by α-Synuclein in multiple system atrophy (MSA) can also occur with Tau pathology (Chin and Goldman, 1996; Tu et al., 1995). Despite these pathological correlations between Tau, α-Synuclein inclusions and perhaps other PD-related genes, there is no known mechanistic connection between them. While the primary Tauopathies and PD have distinctive clinical features, significant overlap exists in the variable appearances of dementia and parkinsonism (Klein et al., 2006). Inflammation is a common secondary denominator in PD. Microglia activation and an increase in astroglia and lymphocyte infiltration are observed in PD. An increase in the number of astroglia (Damier et al., 1993) and dystrophic astrocytes (Braak et al., 2007) are detected in brain autopsies from PD patients. Positron emission tomography also suggests increased glial activation in PD patients (Gerhard et al., 2006). Therefore, PD is a complex disorder that not only involves death of dopaminergic neurons, but may be caused by different genes and mutations, which are confounded with aging, and widespread inflammation in the brain (Block and Hong, 2007; McGeer and McGeer, 2008; Nagatsu and Sawada, 2005).

The identification of inflammatory mechanisms in PD remains a conjecture, primarily in relation to α-Synuclein pathology. Several lines of research challenge the traditional view, which suggests that α-Synuclein-related pathologies, in both sporadic and familial PD, are intraneuronal. Recent studies suggest that neuronal loss leads to release of protein aggregates from neurons into the extracellular space and subsequent activation of microglia (Roodveldt et al., 2008). In PD, the aggregation of α-Synuclein from monomers, via oligomeric intermediates, into fibrils is believed to be the disease-causing toxic mechanism. Recent reports indicate that the accumulation of α-Synuclein can result in the formation of intermediate state oligomers, which lead to neuronal cell death (Danzer et al., 2007; Lee, 2008). Extracellular α-Synuclein is reported to be phagocytosed by microglia (Zhang et al., 2005), and aggregated, nitrated, and oxidized forms of α-Synuclein are shown to induce

microglia activation (Reynolds et al., 2008; Zhang et al., 2005). Extracellular α-Synuclein is suggested to be endocytosed via lipid rafts by GM1 of cell surface gangliosides in BV-2 cells (a microglia cell line) *in vitro* (Park et al., 2009). Phagocytosis of α-Synuclein by microglia is followed by activation of NADPH oxidase and production of ROS (Zhang et al., 2005), suggesting that α-Synuclein-mediated neurotoxicity is enhanced by microglia activation and release of pro-inflammatory cytokines. Nitrated α-Synuclein regulates microglia via $CD4^+$ T regulatory (Treg) cells and protects the oxidative-stress prone dopaminergic neurons in SN (Benner et al., 2008; Kuhn et al., 2006; Reynolds et al., 2008). A direct effect of neuromelanin, which is the pigment present in SN, on activation of microglia through activation of $_{NF}$-$_{K_B}$ has also been reported *in vitro* and *in vivo* (Wilms et al., 2003). More evidence suggest that microglia-derived inflammatory factors such as ROS, NO, TNF-α, and IL-1β can regulate the progression of neuronal cell death in PD (Hirsch and Hunot, 2009), as LPS-mediated neurotoxicity can cause loss of dopaminergic neurons (Castano et al., 1998). LPS injection into the brain increases inflammatory factors, including COX-2 and iNOS, prior to loss of dopaminergic neurons (Hunter et al., 2007). TLR4, the main receptor for LPS, is preferentially expressed on microglia compared to astrocytes (Kim et al., 2000) and neurons, which are unresponsive to LPS in culture models (Saijo et al., 2009). The combination of factors that are produced by activated microglia and astrocytes in turn may promote neurotoxicity, which seems to primarily target dopaminergic neurons in PD. In addition, toxins such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) lead to microglia activation, suggesting that infiltration of $CD4^+$ T lymphocytes may be involved in PD. Dopaminergic toxicity can be mediated by $CD4^+$ T cells and requires the expression of Fas-ligand (FasL) (Benner et al., 2008; Brochard et al., 2009). Taken together, these findings suggest that neuroinflammatory mechanisms and microglia response in PD are contentious. The hypothesis that α-Synuclein is secreted from neurons challenges the premise that LBs are intraneuronal inclusions and extracellular α-Synuclein has not been reported in PD brain patients. Additionally, the emergence of Tau pathology as a risk factor in PD and the detection of inflammation in PD brains without LB formation; e.g., parkin-linked autosomal recessive early onset PD, suggest that α-Synuclein pathology is insufficient to explain inflammation in PD. Further studies to identify communication between neurons that accumulate pathogenic or mutated proteins and brain microglia and astrocytes are needed.

Mechanisms that act to resolve inflammatory responses may be relevant to PD pathology. The chemokine receptor CX3CR1 is present on microglia, and CX3CR1 knockout mice exhibit increased toxicity in response to systemic LPS treatment and increased neurodegeneration in the SN following MPTP administration (Cardona et al., 2006). Additionally, Nurr1 is required for the generation and maintenance of dopaminergic neurons, with rare mutations associated with familial PD. Reduction in Nurr1 levels exacerbates inflammatory responses in microglia and astrocytes, leading to degeneration of tyrosine hydroxylase-positive neurons, suggesting that Nurr1 protects dopaminergic neurons by restraining the activity of microglia and astrocytes (Saijo et al., 2009). Although a role of inflammation is present in the pathogenesis of PD, the general features of inflammation, particularly in the context of innate and adaptive immunity, may considerably differ between PD and AD despite the disproportional overlap in Tau pathology. While the effects of extracellular plaque on neuroinflammation are investigated at the expense of intracellular or pre-plaque Aβ in AD, the multiplicity of genetic variation and mutations, mainly in familial PD, renders the disease a spectrum of disorders that may have to be investigated each in connection with its prospective genetic pre-disposition.

Amyotrophic lateral sclerosis

ALS or Lou Gehrig's disease, is a fatal disease that kills motor neurons in the brainstem, spinal cord, and motor cortex. Genetic heritability in families with adult-onset ALS is associated with several genes such as superoxide dismutase 1 (*SOD1*) (Rosen, 1993), transactive response (TAR) DNA-binding protein (*TDP-43*) (Neumann et al., 2006), and *FUS/TLS* (fused in sarcoma or translocation in liposarcoma) (Kwiatkowski et al., 2009; Vance et al., 2009). Less than 20% of ALS cases are familial associated with missense mutation in SOD1 (Gros-Louis et al., 2006; Rosen, 1993). Transgenic mice harboring human SOD1 mutations reproduce ALS pathology (Clement et al., 2003) and transgenic mice with SOD1 mutations display superoxide dismutase activity, suggesting a gain-of-toxic-function in ALS (Turner and Talbot, 2008). Most ALS cases are sporadic with 50% of patients display coincident deterioration of both motor and cognitive function (Morita et al., 2006; Talbot and Ansorge, 2006) and 20% develop clinical features suggestive of fronto-temporal lobar degeneration (FTLD) (Lomen-Hoerth et al., 2002; Lomen-Hoerth et al., 2003). Ubiquitinated neuronal inclusions are detected in motor neurons of most cases of ALS patients. TDP-43 is a major component of ubiquitinated inclusions in sporadic ALS patients and in patients with FTLD (Neumann et al., 2006). Dominant mutations in the *FUS/TLS* gene are also identified in several ALS families (Kwiatkowski et al., 2009; Vance et al., 2009). The wild-type FUS/TLS protein contains RNA-binding motifs and is believed to be involved in transcriptional regulation (Uranishi et al., 2001; Wang et al., 2008). Like TDP-43, wild-type FUS/TLS is localized to the nucleus under normal conditions, but mutated forms aggregate in the cytoplasm of motor neurons in ALS (Kwiatkowski et al., 2009; Vance et al., 2009). Pathologically, ALS patients have TDP-43 accumulation in motor neurons (Ayala et al., 2005; Neumann et al., 2006) and Tau-negative ubiquitin inclusions identical to those of FTLD patients (Forman et al., 2006). Although no TDP-43 mutations have been associated with FTLD, several mutations (Q331K, M337V, G294A, A90V) have been identified in motor neuron disease (MND)/ALS (Gitcho et al., 2008; Sreedharan et al., 2008). TDP-43 is also altered in AD. A large number (75%) of AD cases show TDP-43 pathology (Amador-Ortiz et al., 2007). LB disorders also demonstrate TDP-43 pathology in AD with LB dementia (LBD), PD and PD with dementia (Nakashima-Yasuda et al., 2007). Co-localization between TDP-43 and NFTs and TDP-43 and α-Synuclein in dystrophic neurites are also identified, despite studies showing lack of co-existence between TDP-43 and Tau pathologies (Arai et al., 2006; Nakashima-Yasuda et al., 2007; Neumann et al., 2007). Therefore, the overlap in gene expression and proteinopathies between ALS and other neurodegenerative diseases suggests common pathological mechanisms.

A common pathological hallmark of ALS is the presence of ubiquitin-immunoreactive cytoplasmic inclusions in degenerating neurons, followed by a strong inflammatory reaction (McGeer and McGeer, 2002). Neuroinflammation is detected in spinal cords from human ALS patients and mouse models of the disease (McGeer and McGeer, 2002). Innate immunity is implicated in the amplification of the inflammatory response in ALS (Letiembre et al., 2009). Chronic infusion with LPS augments the innate immune response and exacerbates pathology in pre-symptomatic ALS mice (Nguyen et al., 2004). CD14, a protein that facilitates TLR4 responses to LPS, and TLR2 are up-regulated in the spinal cords of mice with ALS (Nadeau and Rivest, 2000; Nguyen et al., 2001) and ALS patients (Letiembre et al., 2009; Liu et al., 2009). Expression of mutant SOD1 in microglia leads to ROS production and secretion of TNF-α and the metalloproteinases (ADAM10–17) suggesting a role for oxidative stress in neuroinflammation in ALS (Liu et al., 2009). Injection of mutant SOD1 into the brains of normal or $MyD88^{-/-}$ mice induces an immune response (measured by expression of TLR2 and IL-1β) in the brains of wild-type, but not mutant, animals (Kang and Rivest, 2007), suggesting that mutant SOD1 activates microglia via the MyD88-dependent pathway. It is possible that degenerating neurons in the spinal

cords of ALS patients release ATP that activate glial cells and induce astrocytic purinergic (P2×7) receptors to release IL-1β (Yiangou et al., 2006). In addition, FUS/TLS is a co-activator of NF-κB, and may be involved in the inflammatory response (Amit et al., 2009; Uranishi et al., 2001). Therefore, TLRs and purinergic receptors may serve as sensors for candidate transcription factors, including activator protein-1 (AP-1) and NF-κB. Further investigation is required to better understand the role of inflammation in the CNS of ALS patients. Although inflammation in ALS is characterized by gliosis and the accumulation of large numbers of activated microglia and astrocytes, the major determinants of motor neuron death remains to be established. MHC molecules and complement receptors are highly expressed by reactive microglia in the primary motor cortex and in the anterior horn of the spinal cords of ALS patients (McGeer and McGeer, 2002). Activation of glia is generally marked by increased levels of ROS, inflammatory mediators such as COX-2, and pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6 (McGeer and McGeer, 2002). Motor neurons isolated from transgenic SOD1 mutant mice are more sensitive to Fas- or NO-triggered cell death than wild-type motor neurons (Raoul et al., 2002), suggesting motor-neuron specific cell death mechanisms. Given that astrocytes and microglia produce NO and that astrocytes from SOD1 mutant mice produce FasL (Barbeito et al., 2004), glial cells could directly kill motor neurons. The p75 neurotrophin receptor is also suggested to be involved in ALS-dependent motor neuron death (Pehar et al., 2004).

Gene expression profiling suggests that inflammatory mechanisms are activated prior to motor neuron degeneration, indicating that inflammation may precede the pre-symptomatic phase of the disease (Vargas et al., 2008). Glial cells expressing different SOD1 mutants can have toxic effects on healthy (non-mutated) human motor neurons when co-cultured with them *in vitro* (Di Giorgio et al., 2008; Marchetto et al., 2008). Mutant SOD1, but not the wild-type protein, has been reported to be secreted into the extracellular space via chromogranin vesicles, causing activation of microglia and resulting in motor neuron death in culture (Urushitani et al., 2006). Consistently, mutant SOD1 is detected in the cerebrospinal fluid of ALS patients and it is toxic to rodent spinal cord cultures (Tikka et al., 2002), and intracerebral infusion of mutant SOD1 into wild-type mice induces microglia activation and cytokine production (Kang and Rivest, 2007). However, SOD1 mutations constitute a minority of familial ALS cases and so far there is no evidence for direct binding of extracellular (secreted) mutant SOD1 to microglial receptors. Additionally, neuroinflammation is a cardinal pathological feature in ALS with mutations in *TDP-43* and *FUS/TLS* and in sporadic forms. Inflammation is observed in *TDP-43* and *FUS/TLS*-associated ALS without any evidence for extracellular secretion of these nuclear proteins. One could speculate that misfolded, accumulated or ubiquitinated proteins may play a role in inducing autophagy, so more attention should be paid to glial response to cells undergoing autophagy. If autophagy fails and the cell undergoes apoptosis, the initial inflammatory reaction could also result from extracellular ATP, which is sensed by glial purinergic receptors, released by degenerating neurons (Yiangou et al., 2006). There is also a possibility for the involvement of the adaptive immune response in ALS disease progression. IL-12 is increased in the brains of SOD1 mutant mice that are chronically treated with LPS (Nguyen et al., 2004). Increased levels of $CD4^+$ and $CD8^+$ T lymphocytes and dendritic cells are also observed in close proximity to dying motor neurons in the spinal cords of SOD1 mutant mice and in the brain parenchyma of ALS patients (Mantovani et al., 2009). T lymphocytes infiltration in ALS pathology may have a neuroprotective function (Banerjee et al., 2008; Beers et al., 2008; Chiu et al., 2008).

Fratalkine as a possible inducer of neuroprotection

It is likely that sustained inflammatory responses that contribute to neurodegeneration are mediated by crosstalk between degenerating neurons on one hand, and microglia and

astrocytes on the other hand. One possible mechanism is the release of ATP by degenerating neurons, due to intracellular accumulation of pathogenic proteins (A β, α-Synuclein, Tau, SOD-1 and TDP-43), to activate microglia and contribute to disease progression. Inflammatory responses to intracellular protein accumulation may be an early pathogenic step that can itself influence the secretion of disease-specific proteins to the extracellular space and further exacerbate the inflammatory response. Additionally, the distinct pathways for production and interaction of inducers of inflammation—such as Aβ, Tau, α-Synuclein, mutant SOD1, and TDP-43—and the specific anatomical locations at which these processes occur are likely to determine the specific pathological features of each disease. However, activation of innate immune cells in the CNS, such as microglia and astrocytes, is one of the universal components of neuroinflammation, and they are directly implicated in the pathogenesis of neurodegenerative diseases.

One inducer through which neurons and microglia can communicate is fractalkine (CX3CL1). The chemokine fractalkine and its cognate receptor (CX3CR1) pair play an important role in neuroinflammation and neuroprotection. CX3CL1 is highly expressed in neurons while CX3CR1 is exclusively expressed in microglia within the CNS (Harrison et al., 1998). Exogenously added CX3CL1 is neuroprotective in models of *in-vitro* neuroinflammation (Meucci et al., 1998; Mizuno et al., 2003). Genetic variant with reduced levels of CX3CR1 is associated with age-related macular degeneration in humans (Combadiere et al., 2007). Disruption of CX3CL1-CX3CR1 signaling by deletion of the *Cx3cr1* gene induces neurotoxicity in mouse models of systemic inflammation, PD, and ALS (Cardona et al., 2006) but is protective against neuronal loss in a mouse model of focal cerebral ischemia (Denes et al., 2008) and 3xTg-AD mice (Fuhrmann et al., 2010). In this context, the CX3CR1-deficient 3xTg-AD animals are examined at an age prior to the development of either extracellular Aβ deposition or intracellular Tau aggregation (Fuhrmann et al., 2010) that defines AD, thus, the nature of the signal that mediates neurotoxicity and neuroprotection by CX3CR1 deficiency underscores the role of intraneuronal Aβ in the inflammatory response. Additionally, CX3CR1 deficiency leads to reduced Aβ deposition in two different transgenic mouse models of AD, potentially through enhanced uptake of fibrillar Aβ by CX3CR1-deficient microglia (Lee et al., 2010). Together, these studies suggest that altered microglial signaling through CX3CR1 plays a direct role in neurodegeneration and/or neuroprotection depending upon the CNS insult. CX3CR1 knockout mice show more toxicity and SN degeneration in response to LPS treatment following MPTP administration (Cardona et al., 2006). Furthermore, the inflammatory response triggered by Tau over-expression may mimic inflammatory reactions that can be initiated by intraneuronal Aβ or α-Synuclein, including mechanisms of glial-neuronal communication. In recent studies evaluating the effects of either LPS administration and/or CX3CR1 deficiency on Tau hyper-phosphorylation and aggregation in both non-transgenic mice and in a humanized mouse model of Tauopathy (hTau), LPS administration induced hyper-phosphorylation of both endogenous and transgene-derived Tau that was dependent upon LPS dose and CX3CR1 deficiency. Furthermore, introduction of CX3CR1 deficiency into hTau mice resulted in altered microglia activation, enhanced Tau phosphorylation and aggregation, as well as behavioral abnormalities, suggesting pathways responsible for these effects, including microglia-derived IL-1 and neuronal p38 mitogen-activated protein kinase (MAPK) (Bhaskar et al., 2010). Further examination of CX3CR1 signaling as a possible mediator of neurotoxicity and/or neuroprotection between neurons loaded with pathogenic proteins and glial cells should be further explored.

The ambivalent role of TRAIL in CNS inflammation

Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) has an ambivalent role in neuroinflammation promoting anti-inflammatory mechanisms on one hand, and mediating

detrimental events on the other hand. TRAIL is a type II integral membrane protein and a member of the TNF superfamily with many identified peripheral and CNS functions, including death signaling and immune modulation (Choi et al., 2010; Huang et al., 2005; Pitti et al., 1996; Wiley et al., 1995). TRAIL induces apoptosis by binding to TRAIL-R1 or TRAIL-R2, via formation of death-inducing signaling complex (DISC) (Walczak and Sprick, 2001). Two other TRAIL receptors, termed decoy receptors, including TRAIL-R3 and TRAIL-R4 do not induce death signaling (Degli-Esposti et al., 1997). TRAIL-R3 and TRAIL-R4 seem to block apoptotic signaling of TRAIL (Degli-Esposti et al., 1997). The physiological functions of TRAIL receptors seem to depend on competitive binding (Merino et al., 2006) or formation of heterocomplexes with DISC (Clancy et al., 2005; Merino et al., 2006). TRAIL is not expressed on neurons or resting microglia in the normal human brain, but TRAIL immunoreactivity is detected on oligodendrocytes (Cannella et al., 2007; Dorr et al., 2002). Paradoxically, TRAIL death and decoy receptors are present on neurons, astrocytes and oligodendrocytes in healthy human brain, despite the absence of the cytokine (Cannella et al., 2007; Dorr et al., 2002). TRAIL is produced and released upon activation by a wide range of immune competent cells, including natural killer (NK) and T cells, dendritic cells, macrophages, monocytes and neutrophils (Almasan and Ashkenazi, 2003; Ara and Oliveros, 1992; Cassatella, 2006; Griffith et al., 1999; Kayagaki et al., 1999; Lu et al., 2002; Mariani and Krammer, 1998; Sato et al., 2001; Wolinsky et al., 1976). Activation of antigen-specific T cells decreases the expression level of TRAIL death receptors and resistance to TRAIL-induced apoptosis (Lum et al., 2005).

During immune responses, TRAIL modulates leukocyte function and produces cytotoxicity; however, upon stimulation with IFN-γ, NK and T cells, dendritic cells and monocytes up-regulate TRAIL (Almasan and Ashkenazi, 2003). TRAIL$^{-/-}$ mice exhibit decreased levels of pro-inflammatory cytokines such as Il-12 and IFN-γ in dendritic cells and macrophages (Diehl et al., 2004). Macrophages up-regulate TRAIL in human HIV-encephalitis (HIVE) (Ryan et al., 2004), suggesting that inflammatory insults activate macrophages to produce TRAIL. TRAIL receptors are differentially regulated under pathological conditions such as multiple sclerosis (MS) (Aktas et al., 2003; Cannella et al., 2007), mice experimental autoimmune encephalitis (EAE) (Aktas et al., 2003) and AD (Uberti et al., 2004). MS is a chronic autoimmune disorder believed to be caused by myelin-specific CD4+ Th1 cells, resulting in axonal demyelination in the brain and spinal cord (Arizmendi et al., 1992). EAE is similar to MS and is induced by immunization with recombinant myelin to stimulate encephalitogenic T cells in mice (Aktas et al., 2003). In addition to other regulatory cytokines, TRAIL is released from neutrophils and other leukocytes in bacterial meningitis (BM) (Cassatella et al., 2006). TRAIL is also involved in neurodegenerative disorders such as AD and ischemic stroke (Zipp and Aktas, 2006). In ischemic stroke, microglial activation recruits blood leukocytes, resulting in the growth of the infarct area (Lehnardt et al., 2007; Mabuchi et al., 2000; Prestigiacomo et al., 1999) and TRAIL induces apoptosis following focal brain ischemia (Martin-Villalba et al., 2001; Martin-Villalba et al., 1999). The concentration of TRAIL mRNA increases after transient focal ischemia, whereas immunosuppressive treatment with tacrolimus decreases TRAIL levels, leading to neuroprotection (Martin-Villalba et al., 2001). In AD, TRAIL levels are also increased within the CNS, especially in areas surrounding amyloid deposits (Uberti et al., 2004), and Aβ treatment leads to an increase in TRAIL and TRAIL-R2 levels as well as apoptosis in cell culture (Cantarella et al., 2003). Taken together, these data indicate that TRAIL is produced within the brain upon microglial activation and released from infiltrating blood leukocytes to promote apoptosis in MS/EAE, HIVE, AD and stroke through interaction with TRAIL death receptors. However, the release of TRAIL in MS, AD and HIVE seem to cause apoptosis and contribute to disease pathogenesis, while facilitation of apoptotic clearance prevents TRAIL damage in BM. These findings provide evidence that both beneficial and detrimental mechanisms may occur simultaneously to modulate immune

responses to specific injuries in neurological diseases, thus, underscoring the difficulties to identify a universal role of TRAIL in CNS inflammation. Further investigation is needed to determine the role of TRAIL and its receptors in specific models of neurological diseases.

The failure of anti-inflammatory therapies for CNS injuries and diseases

There is significant evidence that innate immunity may be detrimental to neurons and oligodendrocytes, in stark contrast with other observations that inflammation is beneficial to recovery after CNS injuries. These opposing effects may largely depend on the time or phasic progression of the disease, i.e. early vs. late stage. On the beneficial side, microglia release neurotrophic factors that can induce neuroprotection and contribute to repair after injury. Microglia may also clear cell debris and toxic proteins, preventing their accumulation. Such beneficial effects of innate immune cells are an integral part of planning human clinical trials using anti-inflammatory drugs for CNS diseases. On the harmful side, microglia and other innate immune cells can produce inflammatory markers and induce apoptosis, providing a formidable challenge to balance between beneficial and harmful immune responses and fine-tuning immune cell function. Such a dual effect of the immune reaction to injury and disease raises serious concerns about anti-inflammatory human clinical trials, which entirely failed so far. In the context of stroke or ischemia for example, pro-inflammatory cytokines, microglia activation and leukocyte infiltration are key to determine whether a stroke will lead to reversible ischemic deficits or permanent damage. Inhibition of TNF-α and IL-1, which mediate post-ischemic mechanisms, is neuroprotective in animal models of stroke (Allan and Rothwell, 2001; Allan et al., 2005). IL-1 and TNF-α may modulate the post-ischemic response either directly, by damaging endothelial cells, neurons and glial cells, or indirectly, via leukocytes attraction to the site of injury. The recruitment of monocytes, neutrophils and lymphocytes depends on the early release of pro-inflammatory molecules by resident cells (Wang et al., 2007), so antiinflammatory intervention is time sensitive. However, recruitment of immune cells can have protective effects, as depletion of Treg cells, which can suppress TNF-α and IFN-γ, dramatically ameliorates delayed brain damage (Liesz et al., 2009). Tregs also play an important in reversing Th17 cell-mediated neurodegeneration in a PD mouse model (Reynolds et al., 2010). Considering that inflammation is a common denominator in CNS diseases, targeting the correct timing of an immune response is pivotal to successful designs of human clinical trials.

Other serious concerns exist for the use of anti-inflammatory therapies in AD. It has been demonstrated that innate immune system receptors are involved in the removal of Aβ from the brain. CD14 was shown to interact with the fibrillar $A\beta_{1–42}$ and facilitates its phagocytosis (Liu et al., 2005). Microglia isolated from AD brains reveal up-regulation of CD14 expression and a polymorphism of CD14 receptor is linked to increased risks of AD (Combarros et al., 2005). Activation of TLR2, TLR4 and TLR9 increases the uptake of Aβ by microglia (Chen et al., 2006) (Richard et al., 2008) (Tahara et al., 2006). The expression of TRRs by macrophages is dramatically reduced in AD patients upon stimulation with Aβ (Fiala et al., 2007). These data suggest that the expression of these innate immune receptors may provide a defense strategy to prevent Aβ accumulation in the CNS. However, these receptors fail to remove Aβ from AD brain patients, suggesting that the balance between Aβ production and removal is impaired in AD due to lack of phagocytosis by macrophages and microglia. In AD patients, macrophages do not remove Aβ (Fiala et al., 2007) and mouse models lacking TLR2 display severe cognitive decline (Richard et al., 2008).

Stimulation of the hematopoietic system has also been proposed as a therapeutic strategy for the treatment of AD. Pre-symptomatic AD patients show low levels of macrophage colony-stimulating factor (M-CSF) and other hematopoietic cytokines, predicting development of

dementia (Ray et al., 2007). However, treatment of mouse microglia with M-CSF increases lysosomal degradation of internalized Aβ *in vitro* (Majumdar et al., 2007) and weekly administration of M-CSF into transgenic AD prior to learning and memory impairments protects against cognitive loss (Boissonneault et al., 2009), further suggesting that the failure of antiinflammatory human clinical trials may be due to discrepancy in time between treatment and immune responses in CNS diseases. Nonetheless, these data indicate that targeting innate immune cells has therapeutic potential for neurodegenerative diseases. Anti-inflammatory drugs are beneficial in animal models of AD, and early clinical trials with NSAIDs prior to the development of AD suggested that inhibition of the immune response reduces the risk of disease in humans. However, recent clinical trials using anti-inflammatory drugs not only failed to improve cognition but were harmful in AD patients (Martin et al., 2008). A number of anti-inflammatory drugs were also used in animal models of PD, and human clinical trials using non-aspirin NSAIDs, aspirin, minocycline and other neuroprotective strategies have been similarly disappointing and failed to alleviate the clinical symptoms even in mildly affected human PD patients (Gao et al., 2003). These data raise serious concerns for the general use of antiinflammatory therapies in human CNS injuries and diseases, and it is imperative to better understand the role of immune cells in the CNS. Future investigations should examine the complementary and/or antagonistic mechanistic roles of myeloid cells activation, polarization, recruitment and differentiation.

Conclusion

A major unanswered question is whether it will be possible to safely and effectively target inflammatory mechanisms that contribute to the pathogenesis of CNS diseases. In particular, TLRs and other pattern recognition receptors expressed on microglia are likely to play significant roles in initiating inflammatory responses that are further amplified by astrocytes. Similarly, signal transduction pathways downstream of these receptors that regulate the activities of the transcription factors NF-κB and AP-1 appear to play general roles in mediating the production of amplifiers and effector molecules, such as cytokines (e.g., TNF-α, IL-1β, and IL-6), ROS, and NO. Several of these factors could be general neurotoxic factors for the majority of neurodegenerative diseases. It will be interesting to determine how the output of activated, innate immune cells affects specific types of neurons. For example, many of the same cytokines are suggested to play pathological roles in AD, PD, and ALS, but the patterns of neuronal loss are distinct. It will therefore be important to determine whether this difference reflects different sensitivities of specific neurons to generic neurotoxic factors or the production of neurotoxic factors with neuron-specific activities. Additionally, more effort is required to understand the gene networks that underlie the neuro-protective roles for microglia and astrocytes, and how these networks are altered in chronic disease states. In CNS diseases, the prolonged presence of “danger” signals triggers microglia activation with subsequent production of pro-inflammatory molecules. Although the pro-inflammatory reaction helps to kill and remove dying neurons and cell debris, activated microglia may also damage and remove healthy neurons and thereby substantially contribute to the pathogenic process (Brown and Neher, 2010). A considerable research effort has focused on strategies to suppress microglia activation but with limited success (Glezer et al., 2009). In contrast, less attention has been given to promoting the protective role of microglia, which involves the detection and efficient removal of apoptotic cells (Garden and Moller, 2006; Stolzing and Grune, 2004; Witting et al., 2000). This hypothesis is of critical importance because apoptotic cells can enter secondary necrosis (Silva et al., 2008) and become potent triggers of inflammation (Lauber et al., 2004; Ren and Savill, 1998), leading to further cell damage. An understanding of the factors dictating the switch from a protective to a damaging inflammatory response, and particularly of phagocytosis, will permit interventions aimed at limiting tissue damage.

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