

Why neurodegenerative diseases are progressive: uncontrolled inflammation drives disease progression

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Neurodegenerative diseases are a group of chronic, progressive disorders characterized by the gradual loss of neurons in discrete areas of the central nervous system (CNS). The mechanism(s) underlying their progressive nature remains unknown but a timely and well-controlled inflammatory reaction is essential for the integrity and proper function of the CNS. Substantial evidence has documented a common inflammatory mechanism in various neurodegenerative diseases. We hypothesize that in the diseased CNS, interactions between damaged neurons and dysregulated, overactivated microglia create a vicious self-propagating cycle causing uncontrolled, prolonged inflammation that drives the chronic progression of neurodegenerative diseases. We further propose that dynamic modulation of this inflammatory reaction by interrupting the vicious cycle might become a disease-modifying therapeutic strategy for neurodegenerative diseases.

Introduction

Neurodegenerative diseases are characterized by slow progressive loss of neurons in the central nervous system (CNS), which leads to deficits in specific brain functions (e.g. memory, movement, cognition) performed by the affected CNS region. These neurodegenerative diseases include Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), multiple sclerosis, Huntington's disease and multiple system atrophy. Neurodegenerative diseases usually extend over a decade, and the actual onset of neurodegeneration may precede clinical manifestations by many years. The mechanism that drives chronic progression of neurodegenerative diseases remains elusive. Clearly, if a driving force remains active, therapeutic strategies aimed at neuro-rescue, replacement or regeneration might underperform. Therefore, it becomes critical and urgent to investigate what determines the progressive nature of neurodegenerative diseases. Neuroinflammation (inflammation in the CNS), a prominent feature shared by various neurodegenerative diseases, has been increasingly implicated in these

diseases. However, the nature of its involvement in the disease progression remains unclear.

Is inflammation friend or foe in neurodegenerative diseases?

Inflammation is a complex cascade of self-defensive response to injurious stimuli. Traditionally, the CNS was considered immunologically privileged because of its limited inflammatory capacity and lack of lymphatic infiltration. The latter is attributable to the existence of the blood–brain barrier (BBB), a membrane structure that restricts passage of cells and many substances from blood to brain. However, it is becoming increasingly clear that the CNS actually is immunologically specialized. Microglia, the resident innate immune cells in the CNS (Box 1), provide the first line of defense whenever injury or disease occurs. They can sense a wide range of stimuli that disrupt physiological homeostasis, including CNS trauma, ischemia, infection, toxic insult and autoimmune injury [1–3]. An acute insult to the CNS triggers rapid microglial activation, the principal component of neuroinflammation. Once activated, microglia show a series of changes in morphology (from a resting, ramified shape into an active, amoeboid shape), gene expression, number (increased proliferation of resident microglia and recruitment of bone marrow–derived precursors that infiltrate the CNS) and function (e.g. phagocytosis and production of many different bioactive molecules). Activated microglia produce and secrete a spectrum of inflammatory mediators, such as eicosanoids, cytokines, chemokines, reactive free radicals and proteases [1,4,5]. These inflammatory mediators cannot only further modulate immunologic actions but also act on neurons to alter their function.

Neuroinflammation is now increasingly accepted as a double-edged sword [6]. On one hand, substantial evidence points to detrimental roles of neuroinflammation in neurodegenerative diseases [4,7–9] (discussed below); on the other hand, some observations indicate that inflammation is actually beneficial for recovery in certain circumstances [6,10–12] (Box 2). For example, the resident and bone marrow–derived microglia have been reported to stimulate myelin repair, remove toxic proteins (e.g. amyloid plaques) from the CNS and prevent neurodegeneration in chronic

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Box 1. Microglia

Microglia, a subtype of glial cell, are the prime components of an intrinsic immune defense in the central nervous system (CNS). Microglia are distributed throughout the mature CNS and they constitute ~15% of the total CNS cells. It is now well accepted that microglia are of mesodermal origin and belong to the monocyte-macrophage lineage [1]. During embryological development, a group of myeloid progenitor cells migrate from the bone marrow into the CNS parenchyma where they reside and differentiate into microglia. In adults, the BBB (blood-brain barrier) makes it extremely difficult for the body to constantly replace microglia; in cases of a disrupted BBB, microglia could be replaced with myeloid progenitor cells. Unlike peripheral macrophages, microglia seem to have a very low turnover rate while in their quiescent state [80,81]. Resting microglia exhibit a characteristic ramified morphology. Whereas the small cell bodies remain stationary, their long branches are constantly moving and surveying the surrounding area, and they are very sensitive to small changes in physiological conditions [81]. It allows microglia to fulfill their immune surveillance functions thereby maintaining CNS homeostasis. As an important line of CNS defense, microglia become quickly activated in response to CNS injuries or immunologic stimuli. Activated microglia function similarly to macrophages by undergoing phagocytosis, antigen presentation, rapid proliferation and cytotoxic secretion [81]. Phagocytic microglia (ameboid shape) migrate along a chemotactic gradient to reach the injury site and phagocytose cellular debris or foreign materials; meanwhile, they release chemokines to attract more microglia and secrete inflammatory factors to promote more microglia to proliferate and do the same. Compared with peripheral antigen-presenting cells (APCs) such as macrophages, dendritic cells and B cells, microglia are weak APCs; they must be activated before presenting antigen to T cells that cross the compromised BBB in pathological conditions [82,83]. Different from macrophages, microglial reaction is much more tightly regulated spatially and temporally to maintain a precise immune response and thereby to protect the vulnerable nervous tissue [83]. Activated microglia also interact with astroglia (Box 3) in the facilitation of neuroprotection [6]. However, not all beneficial effects of microglial activation come free of charge, and excessive microglial reaction can become destructive. A variety of cytotoxic substances released by activated microglia can also create considerable bystander damage to neighbouring healthy tissue, although the initial aim of their secretion is to destroy infected neurons, bacteria, and viruses.

CNS diseases [11,13]. Inflammation can also be beneficial for injured CNS tissue by promoting clearance of cell debris and secretion of neurotrophic factors [10,14]. The various molecular mechanisms by which inflammatory mediators affect neurodegeneration (pathologically or protectively) have been reviewed extensively and are not the subject of this article. Instead, we are proposing here that an uncontrolled inflammatory reaction is a driving force of the chronic progression of neurodegenerative diseases.

Uncontrolled inflammation drives the chronic progression of neurodegenerative diseases

Although a well-regulated inflammatory process is essential for tissue homeostasis and proper function, an excessive inflammatory response can be a source of additional injury to host cells. Uncontrolled, excessive inflammation can be the result of either direct immunologic insults (e.g. bacteria, viruses or their products) or a secondary reaction to neuronal lesions from trauma, genetic predisposition or environmental toxins (Figure 1). Because neural tissues have a restricted cell renewal and regenerative capacity, the CNS is extremely vulnerable to uncontrolled autodes-

Box 2. Benefits of neuroinflammation to the central nervous system

Neuroinflammation is a protective response of the central nervous system (CNS) in an attempt to remove harmful stimuli and to initiate a healing process. It is achieved mainly by the activation of microglia and astroglia. Without neuroinflammation, removal of offending materials and recovery from CNS injuries become impossible; thus, progressive destruction of the tissue will compromise CNS function and might cause potentially fatal damage. However, uncontrolled neuroinflammation can become devastating. This is the reason that inflammation is normally tightly regulated by a complex regulating system. A precisely controlled neuroinflammation will benefit the CNS by destroying pathogens, removing cellular debris, eliminating toxic substances, preventing the spread of infections and injuries, releasing neurotrophic factors and promoting tissue repair and regrowth. In the injury site, activated microglia engulf invading viruses, bacteria or other foreign materials as well as dead cells and debris. Activated microglia also secrete numerous cytotoxins including reactive oxygen species, proteases and cytokines to destroy infectious organisms and infected neurons. For example, in Alzheimer's disease (AD), microglia cluster around extracellular senile plaques where they phagocytose and degrade amyloid deposits [84]. In addition to working on eliminating harmful stimuli, inflammation also paves the way for repairing damaged tissue. During inflammation, microglia and astroglia undergo several steps to promote regeneration of neural tissue. These include the secretion of anti-inflammatory cytokines, the recruitment of microglia and astroglia to the damaged site, and the release of neurotrophic factors. Indeed, glia-derived neurotrophic factor (GDNF) has been reported to promote neuronal survival and rescue injured dopamine neurons in several animal models of Parkinson's disease (PD) [85]. In addition, activated microglia physically remove the branches from neuronal perikarya (the neuron cell body) near damaged tissue, which removes synaptic input. This process is called synaptic stripping that facilitates regrowth and remapping of damaged neural circuitry [86]. Moreover, the localized production of chemoattractant molecules, the microglial chemotaxis and the formation of astrocytic scars in the injury site prevent local lesions and infections from expanding widely. Furthermore, coordination among activated microglia, astroglia and neurons plays a pivotal role in repairing tissue injuries and fighting off infections with minimal damage to the healthy CNS cells [81]. It seems that the beneficial effects of inflammation are apparently either inadequate or ineffective in neurodegenerative diseases. A reduction in generating these beneficial effects in response to CNS injuries might remove an important defense mechanism of inflammation and consequently worsen the disease process.

tructive immune and inflammatory processes. To date, a great amount of compelling data indicate that inflammation contributes to the neuronal loss in neurodegenerative diseases but whether or how inflammation decisively affects the chronic progression of these diseases is largely unknown. Using PD as an example for a variety of neurodegenerative diseases, we review the recent literature and hypothesize that an uncontrolled inflammatory process determines the progressive nature of PD and other neurodegenerative diseases. PD is the second most common neurodegenerative disorder, whose characteristics are the progressive degeneration of the nigrostriatal dopaminergic pathway and consequent movement malfunction. Postmortem analysis of the brains of PD patients reveals activated microglia and increased accumulation of inflammatory mediators in the substantia nigra (SN), suggesting the involvement of inflammation in the disease [15].

One of the major stumbling blocks for understanding the mechanisms of the progressive nature of neurodegenerative diseases is the lack of animal models that recapit-

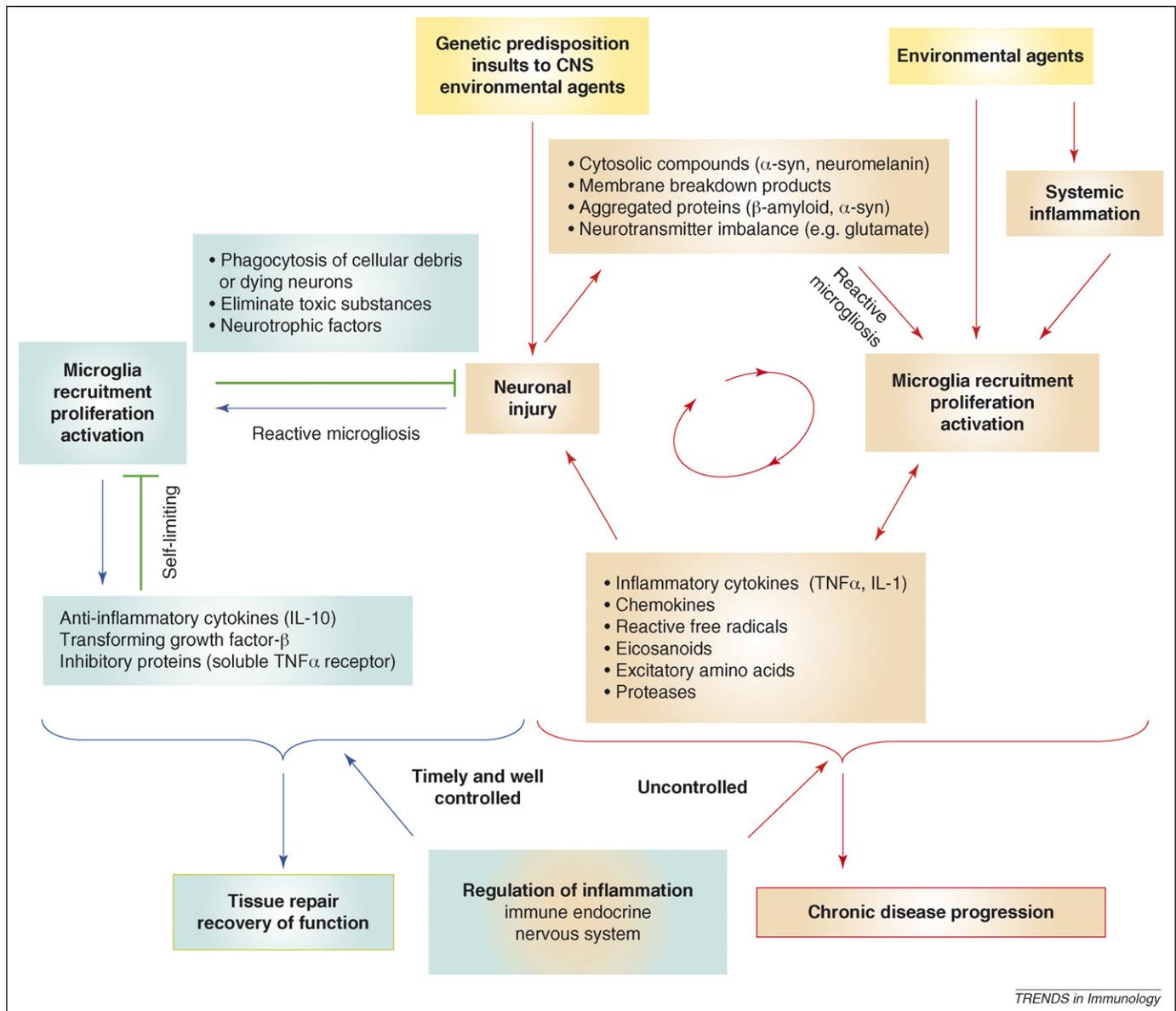


Figure 1. Inflammation determines the progression and outcome of neurodegenerative diseases. Insults to the central nervous system (CNS; e.g. trauma or environmental toxins) or genetic predisposition can directly trigger neuronal lesions. Injured neurons activate the surrounding microglia through noxious self-compounds in the extracellular milieu, such as membrane breakdown products, abnormally processed or aggregated proteins (e.g. α -synuclein and β -amyloid), imbalanced neurotransmitters (e.g. elevated glutamate) and released or leaked cytosolic compounds (e.g. α -synuclein and neuromelanin; highlighted in light orange). Activated microglia produce and secrete a spectrum of inflammatory mediators, such as cytokines, eicosanoids, chemokines, reactive free radicals and proteases. Some environmental risk factors can directly activate microglia or cause systemic inflammation, which might in turn impact on local CNS inflammation, including microglial activation (highlighted in red and light orange). The inflammatory mediators not only can further modulate microglial activity but also can influence the fate of surrounding neurons. Normally, in addition to self-controlling innate immune mechanisms, there is a constant, complex interaction between the immune, endocrine, and nervous systems to maintain proper immune homeostasis. Under strict regulation, inflammation is normally self-limiting and is essential for CNS integrity. Some aspects of the inflammatory process are actually beneficial, such as the removal of cellular debris, the elimination of toxic substances and the release of neurotrophic factors by activated microglia (highlighted in green and blue colors). Escaping from its tight control, the immune response can become exaggerated and destructive, and turns into chronic persistent inflammation that drives progressive neurodegeneration. Thus, regardless of the type of the initial lesion, neuronal damage and uncontrolled inflammation amplify each other, inducing a vicious self-propagating cycle that causes the chronic progression of neurodegenerative diseases. α -syn, α -synuclein; CNS, central nervous system; IL-1, interleukin 1; IL-10, interleukin 10; $\text{TNF}\alpha$, tumour necrosis factor α .

tulate the delayed and progressive nature of these diseases, as well as other key features. Over the last few years, our laboratory has developed both *in vivo* and *in vitro* models that show these critical features and have provided us an opportunity to explore the cellular and molecular mechanisms underlying the progressivity of these diseases. First, the inflammogen lipopolysaccharide (LPS) was used as a representative agent for direct immunologic insults, because LPS has no direct effect on neurons, and its neurotoxicity is entirely dependent on the activation of

microglia. After chronic infusion into the SN, or a single systemic injection, LPS was capable of triggering a chronic inflammatory process and initiating a delayed, progressive degeneration of nigral dopaminergic neurons in rodents [16,17]. Second, the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP, a by-product of synthetic heroin) was used to initiate direct neuronal injury and thereby to induce a secondary microglial reaction, because neither MPTP nor its toxic product 1-methyl-4-phenylpyridinium (MPP^+) can directly activate microglia [18]. The microglial

Box 3. Astroglia

Astroglia (also known as astrocytes) are the most abundant type of glial cells in the central nervous system (CNS). They are of ectodermal origin and are star shaped. Many of their processes enwrap CNS synapses, the junctions between two neurons, which allow neurons to communicate with one another. Interactions between neurons and astroglia are critical for signaling and neuronal integrity. Under physiologic conditions, astroglia provide nutrition and physical support to neurons, maintain ionic homeostasis, buffer excess neurotransmitters, modulate synaptic transmission and secrete neurotrophic factors [87,88]. For instance, astroglia express plasma membrane transporters (e.g. glutamate transporters) and participate in the reuptake and/or release of neurotransmitters including glutamate and GABA (γ -aminobutyric acid), the principal excitatory and inhibitory neurotransmitter in the CNS, respectively [88]. On immunologic challenges and CNS injuries, astroglia become activated. Once activated, astroglia upregulate the expression of cell type-specific proteins such as the glial fibrillary acidic protein, increase the secretion of neurotrophic factors and release several proinflammatory cytokines [6,89]. Among these changes, the elevated release of glia-derived neurotrophic factor (GDNF) is one of the major mechanisms by which activated astroglia exert their neuroprotective effects. In mutual effort to repair CNS injuries, astroglia enlarge and proliferate to fill up the left space after microglial phagocytosis of neural debris [1]. Because of the exceptionally poor ability for CNS neurons to regenerate, this process is thought to be a form of repair. Furthermore, astrocytic scars (a dense glial scar formed by mature, hypertrophic astroglia) wall off the damaged part of the CNS, preventing local injuries and infections from being widespread. However, this beneficial effect is at the expense of impeding potential neuronal regeneration because astrocytic scars provide a physical barrier.

response secondary to direct neuronal lesions is usually termed reactive microgliosis, a process involving increased proliferation, recruitment and activation of microglia. Reactive microgliosis is a common hallmark of neurodegenerative diseases.

MPTP causes parkinsonism in both human and nonhuman primates. The continued presence of activated microglia in their SN >10 years after the last exposure to MPTP [19,20] indicates an active and persistent neuroinflammation in the SN. Because of its selective toxicity to dopaminergic neurons, the MPTP model has been widely used to study the pathogenesis of PD. Taking advantage of long-term cell culture systems, our group demonstrated that, in the absence of microglia (neuron-astroglia co-cultures; Box 3), MPTP induced an acute neurotoxicity that was nonprogressive. By contrast, in the presence of microglia (neuron-glia cultures that contain neurons, astroglia and microglia), MPTP induced enhanced and progressive dopaminergic neurodegeneration [18]. More importantly, dopaminergic impairment induced by either MPTP or LPS was alleviated by pharmacologic suppression of microglial activation or by genetic ablation of various genes encoding proinflammatory mediators [21–24]. For example, blocking microglial activation with minocycline or dexamethasone is neuroprotective in the MPTP model [21,22]. These multiple lines of evidence suggest that excessive activation of microglia (a major component of neuroinflammation) could be a driving force of the PD progression.

The inflammatory exacerbation of neurodegeneration is not particular to PD. Similarly, a great amount of evidence indicates that an excessive inflammatory response correlates with neuronal loss in other neurodegenerative

diseases [8,25,26]. First, epidemiologic studies indicate a possible beneficial effect of long-term use of nonsteroidal anti-inflammatory drugs in both AD (the most common neurodegenerative disease) and PD [27–29]. Second, genetic analyses suggest that DNA polymorphisms of several inflammatory cytokines are a risk factor for AD and PD [30,31]. Third, long-standing pathologic observations reveal prominent reactive microgliosis in the affected brain regions of patients and animal models of various neurodegenerative diseases [26,32]. Fourth and most importantly, experimental evidence shows that the suppression of inflammatory processes mitigates neuronal impairment in both *in vitro* and *in vivo* models of various neurodegenerative diseases [4,21–23]. Taken together, uncontrolled inflammation, either as an initiator or as a secondary reaction, could drive the chronic, progressive neurodegenerative process.

Uncontrolled inflammation and damaged neurons form a vicious cycle causing disease progression

Acute insults to the CNS (e.g. trauma or environmental neurotoxins) can directly trigger immediate neuronal lesions (Figure 1). The critical question is how this initial neuronal damage is transformed into chronic and progressive neurodegeneration. We hypothesize that damaged neurons signal microglia and induce reactive microgliosis; reactive microgliosis further exacerbates neuronal damage by releasing inflammatory and neurotoxic factors. Although it is far from clear what might drive increased inflammation in patients with neurodegenerative diseases, recent experimental work suggests that a spectrum of noxious self-compounds in the extracellular milieu, which are generated after neuronal injury, can serve as stimuli to induce reactive microgliosis. These compounds include, but are not limited to membrane breakdown products; abnormally processed, modified or aggregated proteins (e.g. α -synuclein and β -amyloid); altered molecules (e.g. the active form of matrix metalloproteinase-3); imbalanced neurotransmitters (e.g. elevated glutamate) and released or leaked cytosolic compounds (e.g. α -synuclein and neuromelanin) [33–37] (Figure 1). It seems that the microglial response to these endogenous noxious signals resembles their response to invading microbes [38]. The pattern recognition receptors expressed broadly on microglia can react to these aberrant endogenous ligands in neuronal tissues [5,39]. For instance, we and others have reported that, in neuron-glia cultures, aggregated α -synuclein and β -amyloid exerted potent neurotoxicity through activating microglia [33,36,39,40].

Although a tightly regulated immune response might be sufficient to prevent the deleterious effects of these self-compounds and provide survival signals to injured neurons, the situation is complicated by the poor ability of CNS tissue to tolerate these defensive responses. In addition, the inflammatory response has a self-amplifying nature. Once microglia escape from the strict control normally imposed on them, they lose their defensive features and switch to producing neurotoxic effects [1]. Consequently, a vicious cycle between injured neurons and uncontrolled inflammation occurs inevitably and further contributes to the ongoing pathology (Figure 1).

The neurodegeneration might continue even after the initial offending factors are overcome. Long after MPTP has been cleared from the brain, the SN of MPTP-exposed patients and monkeys displays an active and sustained neuroinflammation and active neurodegeneration [19,20]. Similarly, in AD, the extracellular environment remains hostile to neurons even after the removal of amyloid plaques (an anatomical hallmark of AD) that are an important trigger of AD neurodegeneration [41]. Regardless of the type of initial lesion (inflammation or neurodegeneration), once one process takes place, the other process follows, producing a self-perpetuating vicious cycle that causes the chronic progression that characterizes neurodegenerative diseases (Figure 1).

Mechanistic studies from our group revealed that microglial MAC1 (macrophage antigen complex 1) and NADPH oxidase are both important mediators, bridging neurodegeneration and inflammation in neurodegenerative diseases [33,39,42,43]. Recent experimental observations imply that the adhesion molecule MAC1 (also known as CD11b/CD18, complement receptor 3, or $\alpha_M\beta_2$) might also function as a pattern recognition receptor [39,43–46]. In orchestrating an inflammatory reaction, MAC1 performs diverse functions involved in adhesion, chemotaxis and phagocytosis [47]. In the CNS, MAC1 exclusively expresses on microglia, and its expression is elevated in numerous neurodegenerative diseases including AD and PD [48,49]. We recently reported that microglial MAC1 was indispensable for the enhanced neurotoxicity induced by α -synuclein in neuron-glia cultures [39]. A further study using primary microglia cultures revealed that MAC1-deficient microglia bound significantly less α -synuclein than wild-type microglia [39]. These data suggest that MAC1 might either directly bind α -synuclein, affect microglial phagocytosis of aggregated α -synuclein or both. In addition, we found that MAC1-deficient mice were more resistant to MPTP neurotoxicity [50]. In these mice, the exon encoding the translational initiation codon (ATG) and 15 amino acids of the signal peptide are deleted from the CD11b genomic clone. Neutrophils, macrophages and microglia from these mice have no detectable CD11b/CD18 expression [50,51]. Additionally, microglial MAC1 deficiency greatly mitigated the MPP⁺-induced loss of dopaminergic neurons *in vitro* [50]. Because neither MPTP nor MPP⁺ is able to directly activate microglia, our findings suggest that MAC1 is likely a target for some of the noxious endogenous substances released from the damaged neurons. In further support of this notion, Goodwin *et al.* [42] has reported that β -amyloid (β 25–35) binds to MAC1 and mediates microglial release of NO. MAC1 might also participate in mediating microglial activation via the interaction with fibrinogen, a blood-clotting factor, which gains access to the CNS after BBB disruption in multiple sclerosis [42,52]. Thus, MAC1 might play a critical role in mediating reactive microgliosis and subsequent neurodegeneration in various neurodegenerative diseases.

NADPH oxidase (PHOX), an activity-dependent enzyme complex, is widely expressed in various immune cells including microglia, macrophages and neutrophils. It is a key superoxide-producing enzyme during inflammation. On cell activation, the cytosolic subunits (p47, p67, p40 and

Rac1) translocate to the membrane-bound cytochrome b558 (composed of p22 and the catalytic subunit gp91) and assemble the functional oxidase that catalyzes the reduction of oxygen to superoxide free radical [53]. Superoxide and its downstream products are highly reactive, and excessive production of these radicals can damage proteins, lipids, DNA, or RNA, leading to cell dysfunction and eventual death. Neurons are known to be fairly vulnerable to oxidative stress, and oxidative damage is believed to contribute to the neuron demise in several neurodegenerative diseases. The genetic ablation of NADPH oxidase attenuates the neurodegeneration induced by *in vivo* and *in vitro* exposure to diverse challenges, including neurotoxins (e.g. MPTP, rotenone and paraquat), inflammogen (e.g. LPS), aggregated proteins (e.g. α -synuclein), nanometer size diesel particles and genetic manipulations (e.g. overexpression of mutant superoxide dismutase and amyloid precursor protein in mice as a model of ALS and AD, respectively) [18,21,25,39,50,54–58]. These multiple lines of evidence strongly suggest that the overactivated NADPH oxidase plays a pivotal role in inflammation-mediated neurodegeneration. More importantly, recent evidence has documented that MAC1 is critical for the activation of NADPH oxidase during inflammation [51,59,60]. For example, Coxon *et al.* [51] reported that NADPH oxidase-generated oxygen free radicals are required for MAC1-mediated phagocytosis, and in thioglycollate-elicited neutrophils from MAC1-deficient mice, the phagocytosis and oxidative burst are impaired. Our group also found that, when activated in response to MPP⁺-induced neuronal damage in neuron-glia cultures, MAC1-null microglia produced less superoxide compared with wild-type microglia [50]. Therefore, the coupling between MAC1 and NADPH oxidase might be a central mechanism underlying the reactive microgliosis that mediates immunologic insults and oxidative damage and consequent progressive neurodegeneration. Given their important roles, MAC1 and NADPH oxidase might become a promising target for the development of therapeutic agents halting the vicious cycle between uncontrolled inflammation and damaged neurons and thereby retarding the progression of neurodegenerative diseases.

Regulation of inflammation is a key step in determining the progression and the outcome of neurodegenerative disorders

As discussed earlier, if inflammation exceeds the threshold of CNS tolerability, it might exacerbate the pathology rather than resolve it. In our opinion, in neurodegenerative diseases, the role of neuroinflammation and its ultimate outcome are decided by how the inflammatory process is controlled. A properly regulated and balanced inflammatory reaction is essential for CNS integrity; escaping from the tight control, the immune response can become exaggerated and destructive (Figure 1). Here comes the outstanding question ‘What makes the inflammation flip from a beneficial physiological response to a chronic neurodegenerative one?’. A variety of experimental and genetic insults have been implicated in the pathogenesis of neurodegenerative diseases. The level of insults, the insult period (persistent injurious stimuli), the vulnerability of

individuals (e.g. genetic predisposition) and concurrent events (e.g. other diseases or stressors) likely all affect the reaction of the immune system to insults. Their combined effects along with the regulation of the immune response might eventually decide whether the immune system is able to maintain homeostasis and whether the individual develops a chronic disease. Strong insults to the CNS can trigger acute neuronal damage that in turn can induce an immediate inflammatory reaction. If this inflammatory reaction is timely and precisely regulated and if the insults are stopped or removed, the beneficial effects of the inflammation will overcome its detrimental effects. As a result, the CNS will recover from injury. By contrast, if initial insults cross a certain threshold and become too strong to be overcome by the immune defense, if insults are persistent or if the regulating system of the immune reaction fails, chronic inflammation will occur. Prolonged inflammation is characterized by simultaneous destruction and healing of the tissue. Given the vulnerability of CNS neurons and poor regenerative capacity, the sustained inflammation could drive a chronic neurodegenerative process where detrimental effects of inflammation overcome its beneficial effects. An example supporting this is in multiple sclerosis, a myelin-related protein that has escaped self-tolerance and become an autoimmunogen can serve as the persistent injurious stimulus that accounts for chronic neuroinflammation; therefore, anti-inflammation drugs benefit multiple sclerosis patients.

Accumulating evidence indicates that, in addition to self-controlling innate immune mechanisms, there is a constant, complex interaction between the immune, endocrine and nervous systems to prevent an exaggerated immune response during infection and injury. Activated innate immune cells (including microglia) produce anti-inflammatory cytokines (e.g. interleukin-10 and interleukin-4), transforming growth factor- β and inhibitory proteins (e.g. I κ Ba, silencing nuclear factor- κ B) [38,61–63], all of which play a counterregulatory role in an attempt to resolve the inflammation. Although negative feedback exists in many inflammatory pathways, in neurodegenerative diseases, it might become overwhelmed or undergo age-related failure [64,65]. In these cases, the dysregulated inflammation might become chronic and persistent, especially when accompanied by the continued presence of injured neurons and their toxic products.

Microglia seem to respond differently to the same stimulus if other stimuli precede, co-exist with or follow it. In other words, microglia can be primed or desensitized (negatively primed) by an initial stimulus, which prepares the cells for an enhanced or decreased response to a second challenge. For instance, it has been proposed that microglia in aged or diseased brains are primed, and they are usually committed to generating neurotoxic effects in response to systemic inflammatory signals [66]. Moreover, microglia in older individuals tend to behave differently (e.g. causing an amplified cytokine production after challenge or a diminished cytokine induction with cellular senescence) [67,68]. Matters are further complicated by the fact that aging might adversely affect the viability and self-renewal capacity of microglia. Thus, the mode of microglial activation can crucially affect the initiation,

progression and termination of the inflammatory reaction, and thereby influence the fate of neighboring neurons. In addition, peripheral lymphocytes have been reported to participate in the local response to an acute or chronic CNS insult [69], indicating that cross-talk exists between the innate and adaptive immune systems in pathologic CNS conditions. Furthermore, systemic inflammation might trigger or affect neuroinflammation, leading to an exaggerated secretion of inflammatory mediators in the CNS [17,66,70]. Some blood-borne inflammatory mediators, such as the inflammatory cytokines tumour necrosis factor and interleukin-1 β , can directly inform the CNS of peripheral inflammation by active transport across the BBB or by direct diffusion into the brain through circumventricular organs where the BBB is nonexistent or discontinuous [71,72]. In addition, the BBB may be compromised in neurodegenerative diseases, thus permitting the diffusion of molecules that normally have no access to the brain parenchyma [73]. The complex interplay among multiple signal pathways affects the strength and persistence of the inflammatory reaction, which consequently influences the outcome of diseases. Thus, in neurodegenerative diseases, the role and consequences of the inflammation can change dynamically over time, and the disease course is decided by how the inflammatory reaction is regulated. The dysregulated, persistent inflammation could become a driving force of the chronic progression of neurodegenerative diseases.

Dynamic modulation of the inflammatory reaction might represent a therapeutic strategy for neurodegenerative diseases

With increasing awareness of the detrimental effects of uncontrolled inflammation in the progression of neurodegenerative diseases, pharmacologic targeting of the secondary neurodegeneration mediated by the uncontrolled inflammation could be of therapeutic value for retarding disease progression. Although speculative, it is probable that dynamic modulation of the inflammatory process, based on its early, delayed, acute or chronic regimen and cost-benefit ratio (the risk of adverse outcomes: beneficial outcomes), might represent a novel therapeutic strategy. The key challenge is to determine the optimal strategy based on the cost-benefit ratio for individual patients at a given disease stage.

Because the self-propelling, vicious cycle between injured neurons and uncontrolled inflammation is the driving force leading to progressive neurodegeneration (Figure 1), we hypothesize that any intervention that can interrupt this vicious cycle should be effective in either halting or slowing down the progression of neurodegenerative diseases. The interventions can be achieved by (i) modulation of microglial activity so that inflammation can be dampened to controllable levels and thus becomes beneficial for neuronal survival or (ii) direct improvement of neuronal survival. In support of the former strategy, a plethora of evidence in laboratory animals and *in vitro* cell cultures has shown that pharmacologic inhibition of inflammation correlates with attenuated neurodegeneration [4,21,22,26,74,75]. Furthermore, because of the vicious cycle and the present failure of single drug treatment (anti-inflammation or neuroprotection), drugs

with multiple actions and multi-drug approaches directed at both inflammatory and noninflammatory mechanisms might represent the most promising therapeutic strategies for neurodegenerative diseases. For example, valproate, an anticonvulsant and mood stabilizer, exerts potent neuroprotection in both LPS- and MPP⁺-induced dopaminergic neurotoxicity in neuron-glia cultures through inhibiting microglial activation. Even greater neuroprotection was achieved by the ability of valproate to stimulate the secretion of neurotrophic factors [glia-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor] from astroglia. These neurotrophic factors promote the survival of neurons, which in turn minimizes the intensity of reactive microgliosis [76,77]. In addition to targeting innate immunity, modulation of adaptive immunity has been shown to be beneficial for the control of CNS inflammation. For instance, copaxone, a polypeptide-based therapy approved for multiple sclerosis patients, is thought to promote the development of anti-inflammatory Th2 cells and thereby to dampen the CNS inflammation through the release of anti-inflammatory cytokines and neurotrophic factors [10,78,79]. Copaxone-reactive T cells are also neuroprotective in animal models of ALS and PD [78,79]. However, the strategy to boost the immune reaction (protective autoimmunity) by transplant of immune cells or by exogenous stimuli (e.g. therapeutic vaccines) [7,10] remains controversial and warrants further investigation.

At present, the number of clinical trials concerning the effects of anti-inflammatory drugs on the natural progression of neurodegenerative diseases is too limited to draw a firm conclusion, although there is encouraging experimental evidence [4,21,22,26,74,75]. The low success rate of translating anti-inflammatory drugs from animal models to the human scenario highlights the need for better approaches to anti-inflammatory drug design and more appropriate animal models for preclinical drug screening. In this regard, chronic models are better suited to assessing the progressive nature and to screening the putative disease-modifying therapies.

Conclusion

In neurodegenerative diseases, the role of inflammation can change dynamically over time. Its net effect depends on its regulation and should be judged by its cost-benefit ratio rather than being oversimplified as a 'good' or 'bad' guy for the diseased CNS. It is important to identify the signal pathways that control the initiation, progression and termination of the inflammatory reaction and to unravel the principles of communication between the immune, endocrine and nervous systems. Uncontrolled, prolonged and self-amplifying inflammatory processes may be a common mechanism underlying the self-propelling nature of numerous neurodegenerative diseases. Because of its vital role in pathogenesis, inflammation is a prime therapeutic target for neurodegenerative diseases. The dynamic modulation of inflammatory processes aimed at preventing or interrupting the vicious cycle between damaged neurons and dysregulated inflammation has the potential to emerge as a novel therapeutic strategy. When the inflammatory reaction is beneficial but not sufficient, boosting the

immune system in a well-controlled way might be a choice for neurodegenerative disorder treatment; when inflammation becomes destructive, therapeutic interventions to either suppress inflammation or render it beneficial will become an urgent need.

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