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Pathways towards an effective immunotherapy for Parkinson's disease

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Abstract

Immunizations that target specific types of immune responses are used commonly to prevent microbial infections. However, a range of immune responses may prove necessary to combat the ravages of neurodegenerative diseases. The goal is to eliminate the 'root' cause of neurodegenerative disorders, misfolded aggregated proteins, while harnessing adaptive immune responses to promote neural repair. However, immunization strategies used to elicit humoral immune responses against aberrant brain proteins have yielded mixed success. While specific proteins can be cleared, the failures in halting disease progression revolve, in measure, around adaptive immune responses that promote autoreactive T cells and, as such, induce a meningoencephalitis, accelerating neurodegeneration. Thus, alternative approaches for protein clearance and neural repair are desired. To this end, our laboratories have sought to transform autoreactive adaptive immune responses into regulatory neuroprotective cells in Parkinson's disease. In this context, induction of immune responses against modified brain proteins serves to break immunological tolerance, while eliciting adaptive immunity to facilitate neuronal repair. How to harness the immune response in the setting of Parkinson's disease requires a thorough understanding of the role of immunity in human disease and the ways to modify such immune responses to elicit therapeutic gain. These are discussed in this review.

Keywords

immunization; immunotherapy; neurodegeneration; Parkinson's disease; regulatory T cells; T cells

Next to Alzheimer's disease (AD), Parkinson's disease (PD) is the second most common neurodegenerative proteopathy. They share the common pathologic signature of proteinaceous aggregates comprised of mutated or post-translationally modified proteins, which affect misfolding and increase aggregation. The accumulation of such protein aggregates alters cell function, contributes to neuronal death and apoptosis, and initiates inflammatory responses that contribute to the underlying disease process. In PD and other synucleinopathies, intracytoplasmic protein aggregates, called Lewy bodies (LBs) accumulate both in the CNS and in the periphery [1]. Within the CNS, LBs are found in the substantia nigra pars compacta (SNc), medullary and pontine nuclei, locus coeruleus, amygdala, allocortex, cingulate area and isocortex [2].

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PD is also characterized by the loss of dopaminergic neurons and dopamine [3,4]. Thus, current treatments for PD are specifically aimed at improving motor dysfunction by restoring the loss of dopamine. While levodopa is considered to be the ‘gold standard’ for the treatment of PD [5], patients usually begin treatment with ‘levodopa-sparing strategies’ [6]. After prolonged levodopa treatment, patients commonly develop fluctuations in motor control [7]. While these symptoms can be reduced with carbidopa [8], patients eventually become refractory to treatments [9]. Thus, therapies designed to halt neurodegeneration have been sought during past decades. Such neural repair modalities included growth factors, neural grafts, dopaminergic neuronal replacement via stem cells and immune modulation. All modalities target neural repair in PD, as well as other neurodegenerative proteopathies, yet none of these therapies have been fully realized owing to, in part, significant hurdles.

For example, neurorestorative therapies involving human fetal mesencephalic grafts show modest improvements in motor function and reduce the need for levodopa in most individuals [10,11], with benefits more evident in younger recipients or mild disease [12]. However, up to half of transplant recipients may suffer increased dyskinesia [13,14]. Furthermore, grafts may eventually develop LB inclusions and inflammation [14,15]. These studies suggest that α -synuclein (α -syn) aggregation, LB formation and loss of dopaminergic neurons have underlying degenerative processes that, at least in part, are driven by death mechanisms not yet realized [16]. Additional studies have aimed to improve disease by administering recombinant growth factors or increasing neurotrophins. Although the use of neurotrophic factors to promote neuronal survival and repair has had many successes *in vitro* [17–21] and in animal models of PD [22–24], growth factor therapies for PD have so far been met with limited success. Of the growth factors utilized, GDNF has been the most widely investigated [25]. Experimental observations demonstrated that GDNF positively affects the regeneration of dopaminergic neurons and, as such, is considered to be a realistic therapeutic option for advanced PD. In clinical trials performed thus far, severe adverse events were limited, but disease outcomes were often not changed substantially [26–28]. However, studies delivering GDNF to the putamen demonstrated improvements in clinical scores and decreases in dyskinesia, suggesting that the target area of the brain can significantly affect the outcome of treatments [29,30].

Common among these neuroregenerative therapies, are failures to clear misfolded proteins and to directly address inflammation in the brain and the effects of the innate and adaptive immune systems on neurodegeneration. To these ends, our laboratories have focused on neurorestorative research, utilizing control of the adaptive immune system for dopaminergic neuronal repair. The perils and promise of this approach are outlined in this review.

The immune system & neurodegeneration

Cells of the innate immune system that affect neuronal function include mononuclear phagocytes (MPs; macrophages, microglia and dendritic cells), neutrophils, mast cells, eosinophils, basophils and natural killer (NK) cells [31–33]. MP phagocytose aberrant proteins and cellular debris, secrete both proinflammatory neurotoxic molecules and neurotrophic molecules, and release chemokines that recruit cells of the adaptive immune system to the CNS. The cells use conserved pattern recognition receptors (PRRs), called toll-like receptors (TLRs), which are encoded in the germline and recognize broad pathogen-associated molecular patterns (PAMPs) on pathogens and danger-associated molecular patterns (DAMPs). These are self-molecules released following tissue injuries including those in the brain [34,35]. In neurodegenerative diseases, cells of the innate immune system are activated by DAMPs such as DNA, ATP, hyaluronan aggregates and fibrinogen, as well as modified or misfolded proteins [36]. Unlike the innate immune system, the adaptive immune system is highly specific. Membrane-bound receptors (T-cell receptors [TCRs] and

B-cell receptors [BCRs]) recognize cognate foreign antigens. Recognition of antigen by TCRs in the context of the correct major histocompatibility complex allows for target effector responses via cell-to-cell contact or through soluble factors. B cells can secrete their BCRs as soluble antibodies (immunoglobulin [Ig]), which recognize and bind the pathogen or foreign debris and further aid in their removal by opsonization and activation of complement, increasing phagocytosis and uptake by antigen presenting cells (APCs) that include microglia.

MP neuroinflammation is now accepted as a characteristic of PD and other neurodegenerative diseases [37–42]. Moreover, systemic inflammation is linked to chronic neurodegeneration [43]. Risk factors associated with PD are also associated with inflammation and include aging, rural residence, pesticides, brain injury or encephalitic infection [44]. These elicit reactive oxygen species that are readily linked to nigrostriatal degeneration in PD [41,45]. Thus, initial immunotherapies have targeted inflammation. For example, *in vitro*, NSAIDs were shown to reduce levels of the proinflammatory enzymes cyclooxygenase 1 and 2 (COX-1 and COX-2) [46], and reduce secretion of neurotoxins by microglia *in vitro* [47]. However, while some epidemiological studies suggest that chronic use of some NSAIDs decrease risk for AD and PD, other studies have failed to reproduce these results [48–54]. These reports demonstrate that NSAIDs alone are not sufficient to prevent neurodegeneration, although reduction of inflammation is beneficial. The questions remaining are when to treat, how long and at what dose. These demand further investigation.

Innate immune responses

Microglia are the resident macrophages of the CNS and are continually sampling the local environment [55]. While normally in a quiescent state, they respond quickly to disturbances in their microenvironment and can migrate throughout the brain to areas of insult or injury [56,57]. The engagement of PRRs activates signaling pathways that lead to translocation of NF- κ B and AP-1 to the nucleus where they induce transcription of innate immune proteins. Once activated, they secrete both neurotoxic and neurotrophic factors [58,59], such as the cytokines IL-1 α , IL-1 β and TNF- α [60,61], and neurotrophins, such as NGF and neurotrophin-3 [62,63]. Macrophages clearly have divergent effects [32], and their responses to specific stimuli and cytokines have led to the recent classification of macrophages as ‘classically activated’ (M1), which are more proinflammatory compared with the antiinflammatory ‘alternatively activated’ macrophages (M2) [64]. During chronic inflammation and CNS injury, the neurotoxic effects of microglia overcome the neurotrophic effects [65] and the M1 phenotype predominates [64]. A recent study investigating the polarization of macrophages in spinal cord injury demonstrated that both subsets of macrophages are present, but only M1 macrophages are neurotoxic, while the M2 macrophages promote neuronal repair [66]. These data suggest that modulation of the microglia or macrophage phenotype represents a candidate target for immunotherapies to combat neurodegeneration.

Proteopathies, inflammation & neurodegeneration

Neuroinflammation is seen in many neurodegenerative diseases, while activated microglia have long been recognized to exacerbate disease [31,32,57]. In neurodegenerative diseases, M1 microglia expressing human leukocyte antigen (HLA)-DR and -DQ are associated with the accumulation of aberrant proteins, oxidative stress and neuronal cell death. Reactive microglia have been found in AD, PD, Huntington’s disease and amyotrophic lateral sclerosis, as well as Creutzfeldt–Jakob disease, among other neurodegenerative disease [67–70], and are associated with amyloid plaques in AD brains and LB aggregates in PD brains [71–74].

In PD, the association of LBs and dopaminergic neuron cell death led to the α -syn burden hypothesis [41]. LBs are cytoplasmic inclusions consisting of aggregated and misfolded proteins, such as α -syn, ubiquitin and neurofilament, as well as many other proteins [75–78]. The α -syn present in LBs is often post-translationally modified; thus it may be ubiquitinated [79], phosphorylated [80] and/or oxidized or nitrated [81]. Post-translationally modified forms of α -syn have an increased propensity to aggregate into LBs [82,83], but are also found extra-neuronally in PD brains [84,85] or in the periphery [86]. As demonstrated in animal models and *in vitro* assays, overexpression of α -syn also increases the protein's propensity to aggregate [87,88]. Furthermore, point mutations in the gene encoding α -syn (*SNCA*; OMIM 163890) are linked to parkinsonism [89–92], as are duplications and triplications of the *SNCA* gene [93,94]; all of which increase aggregation of α -syn [95–97]. Taken together, these observations support the α -syn burden hypothesis, which posits that sporadic PD results from the inability to clear α -syn, while familial PD results from the overproduction of normal α -syn or mutated α -syn that prevents or slows clearance. Alternatively, mutations occur in other proteins that normally assist in α -syn clearance, but become defective in this function [41]. McGeer and McGeer further hypothesized that disease can be eliminated with a reduction in α -syn production or prevention of α -syn aggregation [41]. Thus, it is not surprising that vaccines currently being developed for PD target α -syn with the aim to clear aggregated and aberrant forms of the protein. However, there is also much evidence to support a non-autonomous cell death theory, in which cells other than neurons contribute to PD [16].

The substantia nigra (SN) has the highest density of microglia of any brain region [98], and post-mortem studies consistently demonstrate microglial activation in this region in PD. Furthermore, modified and aggregated forms of α -syn present in the PD patient SNc activate microglia. Chronic microglial activation has been seen in mice that over-express human α -syn [99], and *in vitro*, microglia are activated by aggregated human α -syn, leading to increased dopaminergic cell death and increased levels of reactive oxygen species and NADPH oxidase production [100]. In the acute 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of nigrostriatal degeneration, nitrated α -syn (N- α -syn) enhances the neurotoxic activities of microglia, contributing to neuronal death [101]. The elimination of microglia-derived nitric oxide and superoxide are neuroprotective, suggesting that oxidative mediators from activated microglia play a key role in neuroinflammation, neurodegeneration and the accumulation of aberrant forms of α -syn [102]. Indeed, microglia in PD brains are positive for inducible nitric oxide synthase [103], from which nitric oxide-derived peroxynitrite is formed and is available to nitrate α -syn, which in turn and in part, induces neuronal cell death [104]. In addition to reactive oxygen species, activated microglia secrete many other soluble factors, such as chemokines and cytokines. COX-2 is present, as well as increased levels of TNF- α and NF κ B1 in the SN, and IL-15, RANTES and IL-10 levels are significantly elevated in PD brains and in peripheral circulation [105–109]. Cytokines such as IL-1 α and TNF- α secreted by activated glia or endothelial cells increase blood–brain barrier (BBB) permeability [110], which upregulates the expression of cellular adhesion molecules (such as E-selectin) on microvascular endothelial cells [111]. Increased BBB permeability allows activated T cells and B cells to enter the CNS more readily and migrate to the site of neuronal injury [112–114]. Indeed, increased BBB permeability is found in both AD and PD, allowing increased lymphocyte ingress [110,115–117]. In this way, activated innate immune cells of the CNS can affect the adaptive immune system in the periphery and recruit cells to the CNS. In addition, aberrant species of disease-specific proteins, including phosphorylated α -syn, are detectable in tissues outside the CNS in PD and dementia with Lewy bodies patients [86]. The presence of aberrant forms of α -syn in the periphery, such as within the GI tract and draining cervical lymph nodes, presents a possible means for exposure to the protein as a neoantigen and subsequent activation of the adaptive immune system.

Adaptive immune responses

It was once thought that the CNS was an ‘immune privileged’ site, in which immune cells of the periphery could not enter or rarely entered, and thus the two systems had little to no interaction. This hypothesis was supported by the early observation that tissue grafts in the eye or brain survived longer than grafts in other areas of the body [118]. However, evidence for the interaction of the adaptive immune system and the CNS is now well-recognized, and researchers are beginning to harness the neurotrophic effects of the immune system to aid in repair and regeneration in the CNS.

In neurodegenerative disease, CNS proteins may drain to the lymphatic system where the protein is processed and presented by dendritic cells and other APCs to lymphocytes. As proteins associated with neurodegenerative disease are often modified, the immune system may recognize them as non-self, leading to an immune response. An influx of antigen-specific lymphocytes into the brain may exacerbate and perpetuate the activation of microglia near dopaminergic neurons and increase the concentration of neurotoxic molecules within the nigra. Indeed, innate immune system abnormalities have been found in PD and models of PD. Overexpression of human α -syn in a mouse model of PD induces an influx of T and B cells into the CNS with increased proinflammatory cytokines [99]. In MPTP-intoxicated mice, N- α -syn is found in both the brain and in cervical lymph nodes, and immunization with N- α -syn induces N- α -syn specific proliferation of T cells [119]. CD4⁺ and CD8⁺ T cells can be found near dopaminergic neurons in both MPTP-treated mice and in PD patients [120]. Moreover, plasma B cells produce autoantibodies against glia and neuron antigens, and these antibodies are present in the cerebrospinal fluid and serum of PD patients [121,122]. Studies of the peripheral blood from PD patients have also shown many immunological disparities such as decreased naive (CD4⁺CD45RA⁺) T cells and increased memory (CD4⁺CD45RO⁺) T cells [123], increased activated CD4⁺ T cells expressing Fas [124], increased IFN- γ -producing Th1 cells, decreased IL-4-producing Th2 cells and a decrease in CD4⁺CD25⁺ T cells [125]. Altogether, these data suggest that preferential activation of immune cells in PD and immune responses to aberrant forms of α -syn, as well as oxidative stress, affect neuronal cell death, further suggesting the utility of targeted immunotherapies in the treatment of PD [33,41,126].

Immunotherapy for neurodegenerative disease

Immunotherapies are designed to induce, enhance or suppress the immune system for the benefit of the host in the treatment of disease and more recently in neurodegenerative disorders [127–131]. Vaccine therapies have been used for centuries to modulate the immune system’s response to antigens, with the goal of either producing immunity against an infectious disease or attenuating the disease. Vaccines in the traditional sense consist of attenuated or killed pathogens, viral proteins or toxoids to protect against infectious agents. However, in most neurodegenerative proteopathies, no infectious agent is present to target, with the exception of prions. Thus, therapeutic vaccines against neurodegenerative diseases would consist of the self-proteins or peptides derived from the proteins that characterize the disease. Vaccine therapy may evoke active or passive immunity. Active vaccines contain epitopes that elicit immunity or partial protection against the agent from which the epitope is derived. Immunity to the pathogenic agent is achieved upon immunization with the ensuing induction of an immune response and subsequent immunologic memory formation that is specific for the pathogen. For years thereafter, memory immune cells and antibodies specific to the pathogenic agent circulate in the host and quickly respond to the antigen upon reencounter. The response time of immune cells that are primed to the antigen is greatly increased over that of naive cells and is one mechanism by which vaccine-mediated protection is afforded. A therapy targeting the humoral response could aid in the clearance

of α -syn or amyloid- β (A β) by inducing B cells and plasma cells to secrete antigen-specific antibodies. In addition to antibodies that can cross an already permeable BBB, the accumulation of antibodies outside of the CNS and within the peripheral circulation could act as a peripheral sink, reducing the protein load in the CNS by driving the aberrant proteins into the periphery by mass action. The concept of a peripheral sink also makes the infusion of preformed antibodies (passive immunization) against rogue proteins an attractive option for both AD and PD. Indeed, two humanized monoclonal anti-A β antibodies, bapineuzumab and solanezumab, are currently in clinical trials [132]. Other immunotherapies include adoptive transfer and immunosuppression. Adoptive transfer involves the transfer of lymphoid cells from an immune donor to a naive recipient, while immunosuppression simply decreases the number or function of effector immune cells.

As previously stated, most immunotherapies are designed to protect the host from recent or potential exposures to foreign invaders. However, for neurodegenerative proteopathies, the target is self-proteins or modified self-proteins. Thus, the extent and the type of the immune system's response to the vaccine become critical. Excessive inflammation, especially in the CNS, can lead to tissue damage, and chronic inflammation can develop into aberrant autoimmune responses as was seen in the AN1792 clinical trial for AD. This was due in part by the inherent plasticity of CD4⁺ T cells, which can differentiate into Th1, Th2, Th17 or Tregs [133] depending on the microenvironment in which the antigen is recognized and the nature of the major histocompatibility complex-peptide complex. Thus, the response to the antigen can play an important role in the outcome of disease, and most new vaccines are developed with this in mind. Differentiation of naive T cells into Th1 effectors contributes to cell-mediated immunity (activation of macrophages), while Th2 effectors contribute to humoral immunity (activation of B cells). According to the Th1/Th2 paradigm, Th1 cells, which produce IL-2, IFN- γ and TNF- α , are proinflammatory and induce release of reactive oxygen species and nitric oxide by microglia, while Th2 cells that produce IL-4, IL-5 and IL-13 enhance microglial-mediated neuroprotective functions, and thus are considered anti-inflammatory [134]. Both responses may have beneficial effects for neurodegenerative proteopathies, therefore, a balance between the two responses is an important consideration in the design of immunotherapies for neurodegenerative disease.

In preclinical studies for the treatment of AD, using PDAPP mice that are transgenic for human amyloid precursor protein (APP) driven by the human PDGF- β promoter, active immunization with synthetic human A β 42 before the onset of neuropathology prevented the development of plaque formation and gliosis, and vaccination after the onset of neuropathology, slowed progression of disease and as concomitant with the increase in serum antibody titers against A β 42 [135]. Furthermore, intranasal administration of A β peptide lowered A β plaque burden and A β 42 levels in PDAPP mice and was associated with reduced reactive microglia and increased levels of the anti-inflammatory cytokines IL-4, IL-10 and TGF- β [136]. Additional studies with TgCRND8 and Tg2576 mice demonstrated that vaccination against A β reduced cognitive dysfunction with reduced deposition of cerebral fibrillar A β and protected against deficits of learning and age-related memory, respectively [137,138]. Similarly, passive immunization against A β reduced A β deposition in the CNS and A β plasma levels [139,140]. These studies suggested a therapeutic effect of A β 42 vaccination, and after a Phase I clinical trial confirmed its safety, a Phase II clinical trial ensued (AN1792). However, dosing in the Phase II trial was terminated early owing to the occurrence of autoimmune meningoencephalitis in 6% of patients, which was found to be due to Th1-type immune responses [129,141]. Comparing the cytokine profile of peripheral mononuclear cells from patients of the Phase I trial to those of the Phase II trial, it became evident that responses to the vaccine shifted from a Th2 to a Th1 phenotype, which was thought to be due to the addition of polysorbate 80 to the vaccine between the Phase I

and Phase II trials [129]. These data stress the importance of well-controlled immune responses in immunotherapies.

Expert commentary

Immunotherapies for Parkinson's disease

To date, no PD vaccines have been to clinical trial, and relatively few immunotherapies have been developed for preclinical testing. However, of those in preclinical testing, clearance of α -syn and diminution of neuroinflammation represent the major therapeutic strategies. These therapies may improve neuronal survival by decreasing protein aggregates within dopaminergic neurons and by decreasing activation of microglia. In 2005, a preclinical study tested a vaccine against human α -syn ($h\alpha$ -syn) in a mouse model of LB disease [142]. Transgenic mice overexpressing $h\alpha$ -syn that model LB disease were immunized with recombinant $h\alpha$ -syn to increase antibody production and elicit clearance of aggregated $h\alpha$ -syn in the CNS. Immunized mice had elevated $h\alpha$ -syn antibody titers, and while all immunized mice displayed reduced $h\alpha$ -syn load compared with controls, immunized mice producing antibodies with high relative affinity to $h\alpha$ -syn had more pronounced reduction than those with low affinity antibodies. This study also suggested that antibodies against $h\alpha$ -syn are taken up by neurons, bind intracellular $h\alpha$ -syn and increase $h\alpha$ -syn degradation via lysosomal pathways [142]. The work by Masliah *et al.* [142], as well as the studies with AD, suggest that clearance of α -syn represent a viable target, and in 2011 the first clinical trial of a PD vaccine is said to begin. The Michael J Fox Foundation funded the preclinical efficacy testing of the vaccine, PD01, in 2010 by AFFIRiS. PD01 is a mimotope that elicits a highly specific humoral immune response to clear an aberrant form of α -syn [201]. PD01 targets the phosphorylated form of the protein, which activates microglia and induces neurotoxic proinflammatory responses. AFFIRiS claims that PD01 exhibits disease-modifying activity, but the company has yet to publish the preclinical data in a peer-reviewed format [143].

Our laboratory is developing an immunization strategy to clear aberrant forms of α -syn while concurrently controlling neurotoxic inflammatory responses by inducing Treg populations. Tregs are a specialized subset of CD4⁺ T cells that maintain self-tolerance, prevent autoimmunity and maintain immune homeostasis by attenuating inflammation caused by pathogens, injury or autoimmunity [144–151]. In mice, Tregs are identified by CD4 and CD25 cell surface markers and by the transcription factor forkhead box P3 (FOXP3) [152–154]. In humans, they are identified as CD4⁺, CD25⁺, CD39⁺, CD49d⁺, FOXP3⁺ and CD127⁻ [155,156]. While naturally occurring Tregs (nTregs) mature in the thymus, naive CD4⁺ T cells in the periphery can be polarized into the inducible Treg phenotype under certain conditions. The presence of TGF- β , IL-2, IL-10 and all-trans retinoic acid polarize T cells to the inducible Treg phenotype [157–160], and histone deacetylase inhibitors induce proliferation and increase the suppressive function of Tregs [161–164]. Tregs can also be induced by vasoactive intestinal peptide (VIP) [165–167]. Once induced, Tregs promote neurotrophic support by inducing astrocytes to increase expression of BDNF and GDNF [168,169] and may promote glutamate clearance [170]. This is significant considering that astrocyte dysfunction is a known contributor to neurodegeneration [171]. Furthermore, in *in vitro* studies, Tregs suppress effector T-cell (Teff) responses via cell-to-cell contact [150] and with the secretion of soluble factors [172]. Tregs also inhibit the adaptive immune system indirectly by affecting antigen presentation by APCs [173]. Dysfunctional and reduced frequencies of Tregs are associated with several diseases [174] and are being investigated for therapeutic use [167,175–178]. Tregs may also be attractive therapeutic targets in neurodegenerative diseases, as their induction could modulate microglia phenotypes and control adaptive immune responses to CNS proteins. Indeed, works from our laboratory support the utility of Tregs in neuroprotection.

Early studies in our laboratory tested the ability of copolymer-1 (Cop-1; Copaxone[®], glatiramer acetate) as an immunomodulatory agent in a model of PD. Cop-1 is a random polymer composed of four amino acids that induces Th2/Th3/Tr1 cells [179]. The immune response induced by Cop-1 cross-reacts with myelin basic protein [180,181]. Thus, Cop-1 is used as an immunomodulator in the treatment of relapsing–remitting multiple sclerosis, and is thought to work largely by changing the proinflammatory immune response to a more anti-inflammatory response, in part by the induction of Tregs. In relapsing–remitting multiple sclerosis patients, Cop-1 increases Treg frequencies [177], and in mice with experimental autoimmune encephalomyelitis, reduces Th17 frequencies, while increasing Tregs [182]. We tested the immunomodulatory effects of Cop-1 in the acute MPTP-mouse model of nigrostriatal degeneration. Adoptive transfer of splenocytes from Cop-1-immunized mice to MPTP-intoxicated recipients led to T-cell infiltration in the SN, a reduction in microgliosis, an increase in neurotrophic factors and an increase in neuronal survival [169]. The protection provided by the transferred splenocytes was found to be dose dependent, with CD4⁺ T cells providing the greatest degree of neuroprotection [183]. Further investigation provided evidence for the role of CD4⁺CD25⁺ Tregs in the neuroprotection provided by Cop-1-splenocytes transferred to MPTP recipients. Adoptive transfer of CD3-activated Tregs to MPTP-intoxicated mice reduced microgliosis, increased neurotrophic factors and provided greater than 90% protection of dopaminergic neurons in a dose-dependant manner, while *in vitro* assays demonstrated that Tregs modulate the phenotype of microglia and control microglial responses to N- α -syn, lipopolysaccharide and TNF- α with or without phorbol myristate acetate [168]. N- α -syn is immunogenic and vaccination with nitrated-4YSyn (N-4YSyn) elicits an adaptive immune response; 4YSyn is the C-terminal portion of recombinant mouse α -syn that contains four out of five of the nitratable tyrosine residues. Adoptive transfer of T cells from mice immunized with N-4YSyn to MPTP-intoxicated recipients increased dopaminergic neuronal loss [119]. However, when splenocytes from VIP-treated mice were coadoptively transferred with splenocytes from N-4YSyn-immunized mice, a decrease in microgliosis and an increase in dopaminergic neuron survival were observed, while adoptive transfer of splenocytes from mice treated with VIP alone showed only a small increase in neuronal survival, and adoptive transfer of splenocytes from N-4YSyn-immunized mice alone significantly decreased neuronal survival and exacerbated microgliosis. To elucidate which cell types are involved in this process, CD4⁺ T cells were polarized before adoptive transfer, and demonstrated that Th1 and Th17 cells exacerbated the MPTP-induced neurodegeneration. Furthermore, when Tregs from VIP-treated mice were adoptively transferred with splenocytes from N-4YSyn-immunized mice, dopaminergic neuronal survival increased to 96% [184]. Together, these data implicate Th1 and Th17 cells in neurodegeneration and suggest that CD4⁺CD25⁺ Tregs have increased suppressive function in the presence of N-4YSyn-specific T cells.

The abovementioned studies support the utility of Tregs to reduce microgliosis and modulate the adaptive immune response to a neurotrophic phenotype, while reinforcing the therapeutic efficacy of an α -syn vaccine for the clearance of LBs via humoral responses (Figure 1). In disease, proinflammatory M1 microglia predominate, and potentially autoreactive Th1 or Th17 cells exacerbate this phenotype. While M2 microglia may still be present in the diseased brain, the release of reactive oxygen species by M1 microglia and infiltrating macrophages is linked to the accumulation of modified α -syn proteins that contribute to neurotoxicity. An α -syn vaccine designed to elicit a predominately humoral response could induce the production of antibodies specific for modified species of α -syn, which would increase clearance of LBs. The induction of Tregs may ameliorate disease further by modulating the innate and adaptive immune responses as demonstrated in mouse models. Tregs would act by inducing phenotypic switching in T cells, microglia and macrophages or by killing autoreactive T cells, thus supporting a neurotrophic and anti-inflammatory microenvironment. All together, these strategies may decrease the α -syn load

in the CNS and modulate microglia towards a more homeostatic neuroprotective M2 phenotype, thereby increasing neuronal survival and function, and slowing disease progression.

Five-year view

PD is manifest, in part, as a consequence of progressive nigrostriatal degeneration with parallel losses in dopamine and communication links between the SNc and the striatum. Genetic environmental exposure, toxins and aging all contribute. To date, there are only symptomatic treatments available with dopamine replacement therapy or dopamine agonists. A real treatment for disease would involve replacement of damaged neurons and its connections (stem cell therapy), reversal of neural damage (through growth or other neuroregenerative factors) or by engaging the host's immune system to exact repair through natural means. As for the latter, the realization of a neuroprotective immunization strategy remains the lifeblood of our laboratories. How best to control the production of neurotoxic aggregated, misfolded and oxidized proteins that affect free radical formation and tissue damage is difficult. Such proteins are, for the better part, intracellular and released in limited bursts to the extracellular and extravascular compartments. However, its devastating effects on neural connections and neuroinflammation cannot be understated. We posit that effective clearance can be realized through specific antibody and cellular immune responses that can also transform autoreactive neurotoxic T cells into neurotrophic ones. It is our belief that the mechanism by which the immune system can be controlled for therapeutic benefit will be realized in the next decade, and when combined with other treatment modalities, such as neuronal replacement by stem cells and/or growth factors, will change the course of human disease from devastating to controlled and usher in an era where the ravishes of PD are no longer seen.

Key issues

- Aberrant forms of proteins can be immunogenic.
- Immunization against aberrant forms of α -synuclein could affect clearance of Lewy bodies.
- Immunotherapies may be used to modulate or transform the immune system and lead to neuroprotection in Parkinson's disease and other neurodegenerative diseases.
- Immunotherapies for Parkinson's disease are being developed in preclinical studies.

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Patent

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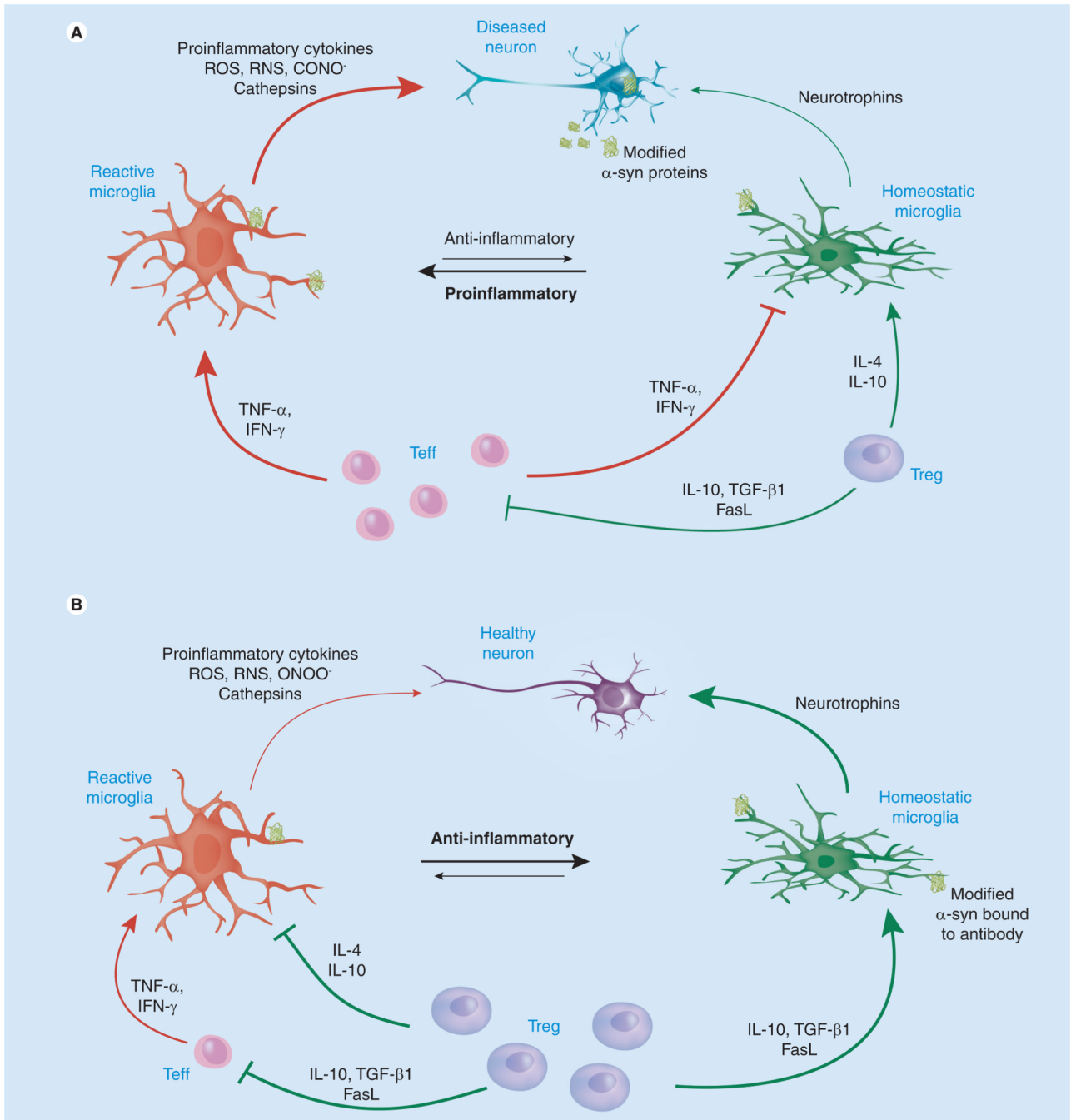


Figure 1. Immunomodulation in Parkinson's disease

In Parkinson's disease, modified α -syn affect microglial immune responses. Reactive microglia secrete neurotoxins, chemokines, peroxynitrite ONO_2^- and other ROS and RNS, which increase the formation of oxidized proteins. Chemokines attract cells of the adaptive immune system, and infiltrating Teffs exacerbate a proinflammatory neurotoxic phenotype by secreting TNF- α and IFN- γ . Tregs may be present in low numbers or are dysfunctional, and thus have a limited affect on disease progression (A). Tregs promote neurotrophic support, suppress Teff responses and secrete anti-inflammatory cytokines, such as IL-10, IL-4 and TGF- β . In the brain of the immunotherapy-treated patient, Treg induction could decrease microglial responses and control adaptive immune activities while supporting the

clearance of misfolded proteins through induction of humoral responses. Thus, the α -syn load in the CNS would be decreased and microglia would switch to a more homeostatic neuroprotective phenotype, thereby increasing neuronal survival and function and slowing disease progression (**B**) [184].

α -syn: α -synuclein; FasL: Fas ligand; RNS: Reactive nitrogen species; ROS: Reactive oxygen species; Teff: Effector T-cell.

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