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Review article

The key role of T cells in Parkinson's disease pathogenesis and therapy

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ABSTRACT

This review focuses on the role of T lymphocytes in the pathogenesis of Parkinson's disease and highlights evidence for modulation of the T cell response as an effective neuroprotective strategy. In preclinical models of Parkinson's disease, modulation of the T cell response results in neuroprotection. Peripheral markers of T cell response show changes in Parkinson's patients relative to controls that have potential application as diagnostic and therapeutic biomarkers. The article also discusses the important immunomodulatory effects of dopamine which may confound study of T cells in patients on dopaminergic therapies, and highlights glatiramer acetate, an FDA-approved therapy for multiple sclerosis that works through modulating the T cell response, as a promising target for translation.

1. Introduction

Parkinson's disease (PD), pathologically characterized by α-synuclein inclusions and dopaminergic cell death and clinically characterized by tremor, rigidity, bradykinesia and gait impairment along with a multitude of non-motor symptoms [1], is the second most common neurodegenerative disease worldwide, accounting for substantial disability and health expenditure [2,3]. The mechanisms underlying the progressive, degenerative aspects of PD are not entirely clear, but several lines of evidence have suggested that immune dysregulation may play a role. Building upon the findings of Foix and Nicolaescu in 1925 [4], McGeer at al detected large numbers of activated microglia in the substantia nigra of PD brain specimens post-mortem that were not seen in controls [5]. Two decades later, T cells were also found in the substantia nigra of PD patients [6]. These observations and others led to the hypothesis that interactions between the microglia (resident macrophages of the central nervous system) and infiltrating T cells shape the pathogenesis of Parkinson's disease.

Under non-pathologic conditions, microglia patrol the CNS for threats and clean up cellular debris. However, interaction with activated T cells can polarize microglia toward a proinflammatory or anti-inflammatory state. A proinflammatory state can be induced by interaction with Th1 and Th17 subtypes of helper T cells and is characterized by production of tumor necrosis factor α (TNFα), interleukin 1 β (IL-1β), IL-6, and expression of inducible nitric oxide synthase (iNOS) among others, while an anti-inflammatory polarization is favored by the presence of Th2 helper or regulatory T cells (Tregs) and can induce production of the cytokines interleukin 4 (IL-4), interleukin 5 (IL-5), interleukin 10 (IL-10), transforming growth factor β (TGF-β) and neuronal growth factors such as brain-derived neurotrophic factor (BDNF) (Fig. 1) [7,8]. It has been shown that exposure to proinflammatory factors released by activated microglia and other stressors can cause the catecholaminergic neurons of the human substantia nigra to express major histocompatibility class I molecules (MHCI) with non-self antigens, becoming vulnerable to attack by cytotoxic $CD8^+$ T cells [9].

Since cross-talk between T cells and microglia influences polarization of the immune response, modulation of the T cell response has great potential as a therapeutic strategy.

The microglial response in PD has been reviewed elsewhere [10–13]. This review focuses on T cells in Parkinson's disease, starting with their role in PD pathogenesis as inferred from animal models, exploring their relationship with genetic variations linked to PD, and moving on to the changes in T cell populations seen in the blood of Parkinson's patients and possible future implications of these markers in diagnosis and therapeutic monitoring. Lastly, we discuss T cell interactions with levodopa and other therapies in current use for PD as well as therapies currently under investigation. We propose that the T cell response is a significant contributor to the pathogenesis of Parkinson's disease and represents an important target for development of clinical biomarkers and neuroprotective therapy.

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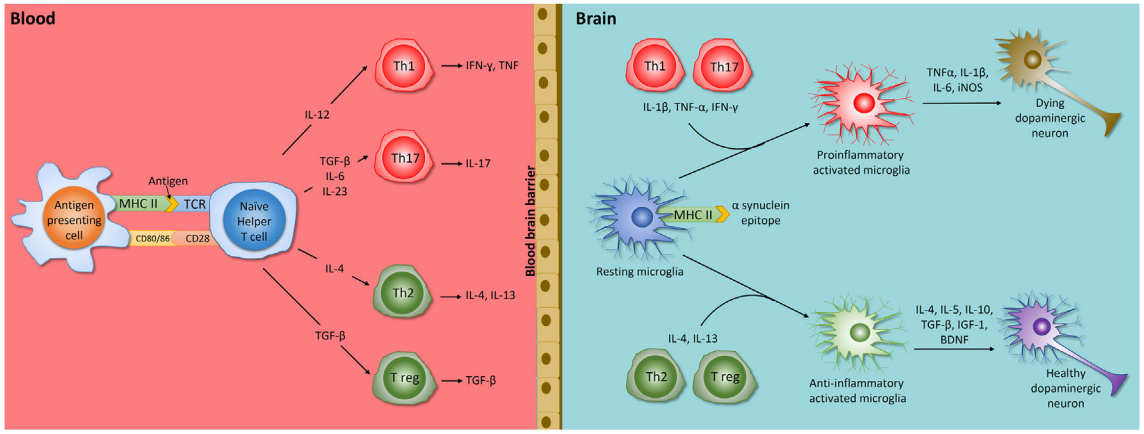

Fig. 1. Naïve helper T cells are activated in the periphery through interaction with antigen presenting cells and differentiate into proinflammatory (Th1, Th17) or anti-inflammatory (Th2, Treg) subtypes influenced by the cytokine milieu. These activated T cells migrate across the blood-brain barrier and interact with resident microglia in the brain, polarizing these cells to proinflammatory or anti-inflammatory states. A proinflammatory state can be induced by interaction with Th1 and Th17 subtypes of helper T cells and is characterized by production of the inflammatory molecules TNF-α, IL-1β, IL-6, and inducible nitric oxide synthase (iNOS), leading to neuronal damage and death. Anti-inflammatory polarization is favored by the presence of Th2 helper or regulatory T cells (Tregs) and can induce production of the cytokines IL-4, IL-5, IL-10, transcription growth factor β (TGF-β) and neuronal growth factors such as BDNF.

2. T cells in animal models of Parkinson's disease pathogenesis

The initial identification of activated microglia and T cells in human post-mortem specimens spurred further research into the role of T cells in animal models of Parkinson's disease, most prolifically in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and adeno-associated virus α-synuclein (AAV-syn) mouse models (Table 1). It is important to note that the T cell activity generated by these toxic and viral vector models may be a reaction to the specific and relatively acute insult delivered to the brain, and may not parallel what happens in the human brain with PD. Inferences about the pathophysiology of human PD must therefore be drawn with caution.

In an acute MPTP model, helper ($CD4^+$) and cytotoxic ($CD8^+$) T cells were seen to infiltrate the substantia nigra of intoxicated mice, and mouse strains deficient in helper but not cytotoxic T cells exhibited greatly diminished MPTP-induced dopaminergic cell death, supporting the hypothesis that the inflammatory T cell response in this model plays a causative role, and is not just a response to cell death/damage by the toxin [6]. The deleterious effect of the helper T cells on neuronal survival involved the first apoptosis signal receptor (Fas) pathway. Many of the findings in animal models underline the role of Tregs in neuroprotection. Aquaporin 4 deficiency increases susceptibility to MPTP toxicity and is also associated with reduced numbers of $CD4^+$ $CD25^+$ Tregs, leading Chi et al. to hypothesize that decreased Treg activity could be leading to increased inflammation and toxicity, although they did not look at whether normalizing Treg function in Aquaporin 4 deficient animals reversed this [14]. The neuroprotective role of Tregs is supported by work from Reynolds et al., who found that $CD4^+CD25^+$ regulatory T cells suppressed microglial activation induced by nitrated α-synuclein while effector T cells had a proinflammatory effect [15]. This group also showed that adoptive transfer of activated Tregs to MPTP intoxicated mice resulted in greater than 90% protection of the nigrostriatal system and upregulation of glial cell derived neurotrophic factor [16]. Most recently, the specific mechanism of Treg-mediated neuroprotection was elucidated by Huang et al., who showed that $CD4^+$ $CD25^+$ Tregs directly protect dopaminergic neurons from MPTP-mediated damage through the interaction of transmembrane proteins CD47 on T cells and signal-regulatory protein α (SIRPA)

Table 1
T cell involvement in animal models of in vivo PD pathology and neuroprotection.

Study	PD model	Intervention	Outcome
Laurie 2007	MPTP mouse	Adoptive T cell transfer from Cop-1 immunized mice	Neuroprotection by Cop-1 conditioned T cells
Reynolds 2007	MPTP mouse	Adoptive transfer of CD3-activated Tregs	Neuroprotection, decreased microglial activation, and up-regulation of GDNF and TGFβ
Brochard 2009	MPTP mouse	Removal of helper T cells Removal of cytotoxic T cells	Neuroprotection from depletion of helper T's No change in toxicity from removal of cytotoxic T's
Chi 2011	MPTP mouse	Aquaporin 4 knock-out (resulting in Treg deficiency)	Increased neurotoxicity, increased microglial activation with Treg deficiency
Chung 2012	MPTP mouse	Bee venom Bee venom + Treg depletion	Neuroprotection, increased proportion of Tregs with bee venom. Neuroprotection by bee venom blocked by Treg depletion
Gonzalez 2013	MPTP mouse	D3R knockout on $CD4^+$ T cells D3R knockout + WT $CD4^+$ T cells	Neuroprotection in D3R knockout No protection when WT helper T cells are added to D3R knockout
Kosloski 2013	MPTP mouse	GM-CSF Adoptive transfer of GM-CSF induced Tregs	Neuroprotection, increased Tregs Neuroprotection by GM-CSF or GM-CSF induced Tregs
Lacan 2013	MPTP mouse	BCG	Upregulation of Tregs and neuroprotection
Olson 2015	MPTP mouse	VIPR2 agonist	Neuroprotection by altering the Th1/Th2 balance toward an anti-inflammatory Th2 response and increasing Tregs
Zhou 2015	MPTP mouse	Rg1 (ginsenoside)	Increased CD4/CD8 T cell ratios, increased Tregs, and neuroprotection
Theodore 2008	AAV2-syn mouse	AAV2-syn innoculation	Increased T cell numbers in the SNpc 2 weeks post-treatment
Harms 2013	AAV2-syn mouse	AAV2-syn inoculation AAV2-syn inoculation + MHCII knockout	Increased MHCII expression by AAV-syn Neuroprotection with MHCII -KO

found on neurons [17].

Although most in vivo evidence of T cell involvement in PD pathogenesis has been gathered in the MPTP mouse model, significant T cell infiltration into the substantia nigra was also seen following targeted overexpression of human α-synuclein through local infusion of the AAV-syn viral vector [18]. While it might be argued for both of these models that the T cell presence observed may not be representative of the immune response in human PD, the demonstration that the pathology is *dependent* upon the presence of $CD4^+$ T cells strongly implicates the adaptive immune system in Parkinson's pathogenesis and provides a compelling rationale for further exploration of immunomodulatory therapies [6,19].

3. Modulation of the T cell response is neuroprotective in preclinical models

Building upon the evidence for the contribution of T cells to PD pathogenesis, numerous successful neuroprotective therapies in preclinical models have shown a T cell mediated mechanism (Table 1). There is especially good evidence that increased numbers or function of Tregs can mediate neuroprotection in the MPTP mouse model. Bee venom prevented MPTP toxicity and was associated with decreased microglial activation and reduction of $CD4^+$ T cell infiltration along with an increased proportion of $CD4^+CD25$ + Foxp3+ Tregs. These effects were not seen in mice depleted of Tregs, suggesting that these cells are necessary mediators of the neuroprotective effect [20].

Bacillus Calmette-Guerin (BCG)-induced neuroprotection in the MPTP model was also mediated by the induction of CD4+Foxp3+ Tregs [21], and neuroprotection by the ginsenoside Rg1 was associated with increased CD4/CD8 T cell ratios as well as increased $CD4^+CD25$ + Foxp3+ Treg populations [22]. Granulocyte-macrophage colony-stimulating factor (GM-CSF), a lymphocyte growth factor, upregulated $CD4^+CD25$ + Foxp3+ Tregs and protected neurons from MPTP toxicity, and adoptive transfer of GM-CSF induced Tregs was shown to be protective as well [23]. A vasoactive intestinal peptide receptor 2 (VIPR2) selective agonist, which increases GM-CSF transcripts in helper T cells and promotes a Th2 anti-inflammatory response, was also shown to be neuroprotective in MPTP mice [24].

One of the most attractive aspects of harnessing the T cell response as a therapeutic approach is that a therapy can be given peripherally to influence T cells that subsequently migrate into the substantia nigra. One such therapy is glatiramer acetate, which is composed of random sized polymers of four amino acids glutamic acid, lysine, alanine and tyrosine, and is FDA approved for the treatment of multiple sclerosis (MS), after Copolymer-1, a very similar compound, was found to be effective in suppressing experimental autoimmune encephalomyelitis, the animal mode of MS. Glatiramer acetate appears to act by inducing the formation of Th2 cells in the periphery that migrate across the blood brain barrier and exert anti-inflammatory and neurotrophic effects in the CNS, and has been shown to improve Treg function in patients with MS [25]. Using a neurorestoration (and not protection) study design, in which glatiramer acetate treatment is started following progressive treatment with MPTP, our group demonstrated recovery of motor function and a nearly complete restoration of striatal dopamine terminals. We also report an increase in the number of dopamine cells in the substantia nigra pars compacta, which is correlated with a glatiramer-induced decrease in activated microglia and an increase in BDNF compared to the MPTP-only treated group [26]. Another group has demonstrated that adoptive transfer of T cells from Copolymer 1-immunized mice spleens and lymph nodes also protected the nigrostriatal system from MPTP mediated toxicity [27].

4. Genetic links support a causal role of neuroinflammation in PD pathogenesis

Functional links to the genetic mutations that cause PD provide further evidence for the importance of T cells in Parkinson's pathogenesis. LRRK2, a gene with mutations linked to late onset PD, encodes a common constituent of helper and cytotoxic T cells that is upregulated in response to immunological threat [28]. Abnormal LRRK2 activity can alter bone marrow myelopoiesis, peripheral myeloid cell differentiation, and intestinal immune homeostasis [29]. PINK1 and Parkin, two mitochondrial proteins with mutations associated with early onset PD, were found to actively inhibit mitochondrial antigen presentation [30]. In the absence of these proteins, inflammatory conditions triggered mitochondrial antigen presentation in immune cells, supporting a role of PINK1 and Parkin as suppressors of an immune response-eliciting pathway provoked by inflammation. The authors of this study hypothesize that increased presentation of mitochondrial “non-self” antigens could contribute to the destruction of dopaminergic neurons by cytotoxic ($CD8^+$) T cells. PINK (-/-) T cells were found to be less effective at suppressing bystander T cell proliferation under conditions favoring Treg polarization [31]. Further evidence for the immunosuppressive role of these proteins and the role of innate immunity in PD pathogenesis was recently published by Sliter et al., who found a strong inflammatory phenotype in both PRKN (parkin) and PINK1 knockout mice as well as PRKN mutator mice that accumulate mitochondrial DNA mutations and develop motor defects and dopaminergic neuronal loss with age [32].

T cells transition from naïve to activated states through recognition of MHC II molecules loaded with their cognate antigens on microglia and other antigen-presenting cells. Differences in the genetic code (known as Human Leukocyte Antigen, or HLA) for these MHC molecules will result in MHC II molecules that present certain antigens, such as α-synuclein epitopes, more or less effectively to T cells. Increased presentation of α-synuclein epitopes increases the probability of a T cell specific activation. It follows that HLA genotypes would impact Parkinson's risk, and indeed common variations in the HLA region have been associated with altered risk of developing Parkinson's disease in several genome-wide association studies. Hamza et al. found peak PD association with rs3129882, a noncoding variant in HLA-DRA, and this was confirmed by Wissemann et al., who also found increased odds of developing PD with the rs2395163 variant of HLA-DQ and decreased odds associated with HLA alleles C(∗)03:04 and DRB1(∗)04:04 [33,34]. The importance of the MHC II antigen-presenting molecule is underscored by the findings of the Standaert group. In the AAV2-syn mouse model, expression of full-length human α-synuclein caused striking induction of MHC II expression by microglia. Knock-out of MHC II prevented a-synuclein induced microglial activation, antigen presentation, IgG deposition and the degeneration of dopaminergic neurons [35]. In summary, the genes LRRK2 and PINK1 that have previously been linked to Parkinson's disease influence T cell function, and genetic differences in HLA alleles that impact microglial antigen presentation to T cells are associated with differences in PD risk.

5. Changes in peripheral T cell markers in Parkinson's patients

Although the healthy CNS is relatively sheltered from peripheral immune responses, evidence suggests that the blood brain barrier in Parkinson's disease becomes more permeable, with significant crosstalk and migration between peripheral and CNS immune cells [36]. While we do not yet have good methods to study the in vivo T cell response within the tissue of the CNS, there is mounting evidence of changes in peripheral T cell populations in Parkinson's patients that have potential for use as biomarkers of disease or outcome measures for human trials of immunomodulatory therapy (Table 2).

Studies of peripheral T cell populations have consistently shown lower total T cell populations in PD patients [37], with the most significant decrease in the $CD4^+$ helper T cell subtypes [38–42] and a decrease in naïve T cells that have not been exposed to their antigen [42–44]. Increased levels of Fas death receptor expression have been found on these T cell populations in PD, suggesting that decreased

Table 2
Summary of peripheral T cell changes in PD patients (studies in chronological order).

Study	Population	Findings in PD patients
Fiszer 1994	25 PD (17 treated) 11 patients with other neuro disease 12 patients with tension headache	Decrease in naïve T cells
Chiba 1995	42 treated PD patients 20 controls	Increased adenosine deaminase (role in function and maturation of T lymphocytes) Increase in activated T cells No correlation with HY stage
Bongioanni 1997	35 untreated PD 35 controls	Increased TNFa expression on T cells (Increased activation)
Bongioanni 1997	35 untreated PD 35 controls	Decreased IFNg expression on T cells (Increased activation)
Bas 2001	30 untreated PD 34 treated PD (Ldopa ± dA, MAO-B) 38 controls	Decreased total helper T cells Decreased naïve helper T cells Increase in activated helper T cells No major differences between treated and untreated PD No correlation with UPDRS or disease duration Decreased naïve T cells with age in PD and controls
Hisanaga 2001	40 treated PD (mean age 68.9) 22 controls (mean age 60.4) 33 patients with mild cerebrovascular disease	Decreased total T cell number Increased proportion of CD4 bright CD8 dull cells
Baba 2005	30 untreated PD 34 treated PD	Decreased helper T cells Increased IFNg/IL-4 ratio (proinflammatory) Independent of L dopa
Rentzos 2007	41 PD (20 untreated, 9 L-dopa, 12 DA or DA + L-dopa) 19 controls	Increased level of RANTES (T cell chemoattractant) Correlation with UPDRS score, disease duration, and treatment status
Rosenkranz 2007	30 PD (4 untreated, 26 treated) 29 AD 33 Age-matched controls 38 Young controls	Increased Tregs with age No difference in Treg numbers between PD patients and age-matched controls Trend towards higher Treg activity in PD patients
Calopa 2010	89 PD (36 untreated, 53 treated) 33 controls	Decreased total helper T cells Decreased naïve helper T cells Increased activated helper T cells No correlation with PD duration or treatment status
Gruden 2011	32 PD patients (treated) 26 controls	Decreased helper T cells Decreased cytotoxic T cells
Stevens 2012	88 PD 77 Controls	Decreased helper T cells Longitudinal decrease in memory T cells (2% loss/year of disease)
Saunders 2012	113 PD 96 Controls	Increased effector T cells correlated with higher UPDRS Decreased Treg function
Chen, Y. 2015	60 PD 40 Controls	Increased Th1, Th17 subsets Decreased Th2, Treg subsets Increased Th1 number and Th1/Th2 ratio associated with increased UPDRS Part III
Chen, S. 2017	18 PD 18 Controls	Increased Th17 subset

numbers may be secondary to apoptosis [42]. This decrease in helper and naïve T cell populations is paralleled by a relative increase in activated T cell subtypes [38,42,45–48]. Proinflammatory polarization in PD is also supported by an increased IFNγ/IL4 ratio [39], as well as increase in proportion of inflammatory Th1 and Th17 subtypes in PD patients relative to controls [49,50]. Tregs are felt to play an important neuroprotective role and generally increase with age in healthy subjects [51]. While one group found no difference in $CD4^+$ Foxp3+ Treg numbers between PD and controls [51], others found decreased $CD4^+CD25^+CD127$- Treg numbers in PD patients [50] as well as diminished $CD4^+CD25^+CD127$-Treg function [48].

The Cohen group first demonstrated the immunogenicity of β-synuclein peptides, raising the possibility that specific immune reactions to this protein might influence disease course in PD [52]. In a recently published study, Sulzer et al. found that peptides from two regions of α-synuclein produced T cell responses in patients with PD [53]. It is important to note that while the mean T cell response differed between PD cases and controls, there were PD cases without response to these peptides, as well as control cases with synuclein-specific T cell response.

Several studies have found correlations between peripheral T cell markers and clinical measures of PD duration and severity. Memory T cells were found to decrease with disease duration in PD patients at a rate of 2% per year [41]. Increased numbers of proinflammatory Th1 cells correlated with higher UPDRS motor scores [38] and higher levels of RANTES (Regulated on Activation, Normal T cell Expressed and Secreted, aka CCL5), a T cell chemoattractant, were correlated with increased motor dysfunction (UPDRS) and disease duration [54]. While these studies support the overall hypothesis of this review, it is important to note that two clinical studies did not find correlations between activated T cell numbers and Hoehn and Yahr stage [45], or UPDRS and disease duration [38].

Alberio and colleagues describe differences in the T cell proteome with lower levels of β-fibrinogen and higher levels of transaldolase isoforms in PD patients relative to controls, and used panel of protein biomarkers as a “PD signature” to successfully classify known PD and control cases as well as to differentiate between early onset and late onset PD cases [55,56]. Further work is needed to validate this biomarker panel in a larger, more heterogeneous cohort of subjects with a variety of ethnic backgrounds and clinical phenotypes, however the potential applications of this protein signature for early diagnosis and possibly measurement of PD progression are exciting.

6. Dopamine/T cell interactions

L-dopa, given orally and converted centrally into dopamine, is the cornerstone of symptomatic therapy for Parkinson's disease along with the dopamine agonists. While not commonly considered immunomodulatory therapy, there is growing evidence that central and

peripheral dopamine levels may impact the immune response.

Not surprisingly, the interaction between dopamine and T cells is complex and depends upon dopamine's concentration, the T cell activation status, the T cell type and subtype, and the specific dopamine receptor subtypes expressed on the cell surface of the T cells [57]. At low physiologic concentration (10 nM), dopamine activates normal resting human T cells and induces T cell adhesion to fibronectin, which allows extravasation into tissues [58]. In the presence of dopamine released by antigen-presenting cells in vitro, T cells are polarized toward an anti-inflammatory Th2 differentiation, while in the absence of dopamine release by APCs, proinflammatory Th1 differentiation is favored [59]. The pro- or anti-inflammatory effects of dopamine on T cells also depend on which receptor is stimulated; binding to D2 receptors induces anti-inflammatory IL-10 secretion while stimulation of D3 and D1/D5 receptors promotes pro-inflammatory TNFα secretion [60].

Increased expression of D2-like receptors on the immune cells of schizophrenic patients compared to controls has been reported [61,62]. D3R mRNA levels were found to be higher in drug free schizophrenic patients than in treated patients [63]. Schizophrenic patients who were medication-naive (first onset) or medication-free had a higher peripheral Th1/Th2 (IFNɣ/IL-4) cytokine ratio than healthy controls, suggesting a pro-inflammatory shift, that was attenuated by 8 weeks of effective neuroleptic (primarily D2-blocking) treatment [64].

In Parkinson's disease, changes in the expression of dopamine receptors and their signaling pathways in T cells are also associated with altered immune function, although the findings at this point are somewhat contradictory [65]. In the MPTP mouse model, expression of the D3R dopamine receptor on $CD4^+$ helper T cells favors a proinflammatory state, promoting Th1 and Th17 responses and decreasing Th2 responses, and is necessary for the pathogenesis of MPTP induced parkinsonism [66]. [67] Surprisingly, in Parkinson's patients there is a decrease in D3R dopamine receptor mRNA that correlates with disease severity, with reduction of D3R binding sites on peripheral lymphocytes [68].

Decreased central levels of norepinephrine, a dopamine metabolite, have also been implicated in PD pathogenesis and extensive neuronal loss in the nucleus coeruleus is seen post-mortem [69]. Infusion of L-dopa has been demonstrated to increase central norepinephrine levels in a mouse model of PD [70], and downstream effects on adrenergic receptors have been implicated in the pathogenesis of L-dopa associated dyskinesias [71]. Norepinephrine receptors of the β2 adrenergic subtype are found on all naïve and Th1 differentiated $CD4^+$ T cells, and similarly to dopamine, norepinephrine can either potentiate or inhibit T cell function depending on the cell subtype and timing of the exposure [72].

In patients under long-term treatment with L-dopa or dopamine agonists, dopaminergic stimulation changes the T cell proteome with an especially interesting dose-dependent downregulation of a protease involved in the degradation of oxidatively modified proteins [73]. Carbidopa is given in conjunction with levodopa to block peripheral conversion to dopamine, and this drug was shown to inhibit T cell activation in PD [74]. While no effect of dopaminergic treatment was seen on peripheral T cell subtypes in several studies [38,39,42], plasma levels of the T cell chemoattractant RANTES were decreased in dopamine agonist and/or levodopa treated patients [54]. In conclusion, although the interactions between dopamine and the immune system are complex and at this point poorly understood, it is important to note that dopaminergic agents may have additional immunomodulatory effects [59] that may influence the success of immunotherapy in Parkinson's disease patients.

7. Discussion/conclusion

Although there is established evidence that T cells, microglia and inflammatory cytokines are present in the substantia nigra of PD patients [4,5,75] debate still exists on whether this inflammatory milieu is a response to ongoing neurodegeneration or a contributor to the pathology. In a new model of sporadic PD, mice lacking the anti-inflammatory cytokine interferon beta exhibited spontaneous neurodegeneration with motor and cognitive impairments and Lewy body pathology in the absence of disease-causing mutant proteins, supporting our hypothesis that inflammation is a cause rather than an effect of PD pathology [76].

Based on the evidence reviewed above, we hypothesize that T cell differentiation shapes the inflammatory cascade in Parkinson's disease and influences whether microglia are polarized to help clear α-synuclein and repair cellular damage or participate in dopaminergic cell death and perpetuate a neurotoxic, proinflammatory environment. Evidence is building that the specific T cell response to α-synuclein, influenced by genetic variations in antigen presentation molecules, may be the instigating factor that converts the normal healthy coexistence of neurons and α-synuclein into a pathogenic relationship. The neurotrophic factors secreted by Tregs and by anti-inflammatory activated microglia can help to restore function after damage has been done, so that immunomodulatory therapies that promote Th2 and Treg response have potential to not only protect, but to restore neuronal function. The efficacy of glatiramer in a neurorestoration model provides further support for this conclusion [26]. This therapy is already FDA-approved for treatment of Multiple Sclerosis, has a benign side effect profile, and is a promising target for translation into PD patients.

While thus far the peripheral changes in T cell subclasses are not well-characterized enough to be diagnostically useful, the T cell proteome “signature” may prove useful in the early diagnosis of PD, and RANTES has potential to be a useful marker of therapeutic efficacy in immunomodulatory trials, especially once the magnitude of change with normal aging and disease progression in these markers is better established. The influence of dopamine on T cell activation is complex, and it is important to consider that dopaminergic therapies may have confounding effects on the immune system and on T cell activation when designing clinical trials in PD patients.

In conclusion, the last few decades of Parkinson's disease research have produced an enhanced understanding of the neuroinflammatory basis for this neurodegenerative disease, and in particular the investigation into the role of T cells in the immune response has shed light on the possible instigating factors of this pathology. We still lack disease-modifying therapy for Parkinson's disease, however the success of T cell mediated neuroprotective therapies in animal models coupled with growing evidence of a similarly proinflammatory T cell response in human PD patients suggests that when harnessed correctly, the T cell response has potential to slow or halt the damage ongoing in Parkinson's disease while promoting neuronal repair and restoration.

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