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Roles for the adaptive immune system in Parkinson's and Alzheimer's diseases

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Abstract

Neurodegenerative diseases, such as Parkinson's and Alzheimer's, affect millions of people and pose major personal and socioeconomic burdens. The causes of neurodegeneration are mostly unknown, although current efforts have described an autoimmune aspect to these diseases. Here we discuss recent findings that shed light on the involvement of the adaptive immune system in Parkinson's and Alzheimer's diseases, and provide a model and outlook for further investigation of T cell responses in neurodegenerative disease. We focus on the identification of T cell epitopes from proteins involved in disease pathogenesis and describe the identification of α-synuclein specific epitopes in Parkinson's disease which provided a crucial link between disease susceptibility and T cell recognition.

Introduction

Inflammation is pervasive in neurodegenerative diseases, including Parkinson's (PD) and Alzheimer's (AD). Here, we focus on evidence, mostly accumulated during the last decade, for a role of the adaptive immune response by T cells in PD and AD. Recent studies from our group have identified α-synuclein (α-syn)-derived T cell epitopes that are preferentially recognized by PD patients, as well as T cells in regions attacked in PD, suggesting an autoimmune component to PD [1••]. T cells also localize to the areas of degeneration in AD and recognize amyloid; but studies of their epitope and patient specificity are preliminary. We propose a model for development of neurodegenerative disease specific T cell responses

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to assist ongoing research. Understanding the function of the adaptive immune system in neurodegenerative pathogenesis promises novel diagnostic markers and treatments.

The case for an inflammatory and immunological component in neurodegenerative diseases

The neurodegenerative diseases of older age, including AD and PD, are major burdens to society, families, and individuals, particularly as the average life expectancy has increased. AD and PD, as well as many other neurodegenerative disorders, exhibit the loss of neurons in the central nervous system (CNS), but the means by which this occurs remains unknown [2]. These disorders also exhibit the abnormal accumulation of high levels of specific aggregated proteins [3].

In the case of PD, while multiple populations of catecholaminergic and cholinergic neurons die over the disease course in the central and peripheral nervous system, the movement disorders are mostly due to the neuromelanin-containing dopaminergic neurons of the substantia nigra [4,5]. The classical pathological aggregate observed in PD brain is intracellular aggregated α-syn protein in Lewy bodies and neurites [5].

The defining pathological aggregates found in AD brain are extracellular “plaques” composed of insoluble amyloid-β (Aβ), a secreted peptide derived from the amyloid precursor protein, and intraneuronal “neurofibrillary tangles” aggregates of highly phosphorylated tau, a protein associated with microtubules in axons [6]. The deposition of tau and Aβ aggregates and neuronal loss in AD are thought to typically begin in the frontal and temporal cortical lobes, and progresses slowly throughout the neocortex and limbic system [6,7].

There is a high degree of overlap in neurodegenerative disorders of aging, where some neurons are lost in both AD and PD, as well as other diseases such as multiple system atrophy [8]. There are moreover multiple additional aggregated proteins that are found in multiple diseases, including TDP43, and many patients and studies indicate most older individuals show some aggregation of several such proteins, which may propagate in characteristic fashion depending on the disorder [8].

Reports of inflammation via the innate immune system, consisting mostly of increased levels of cytokines and activation of antigen presenting cells, has long been observed in these disorders [2,9,10]. New findings implicate a role forT cells that recognize disease related antigens, and may parallel the damage to oligodendrocytes by the acquired immune system in multiple sclerosis [11]. To date, these insights have mostly focused on PD, and as detailed here, but also apply to AD, and may well extend to other CNS disorders, including amyotrophic lateral sclerosis (ALS), that feature inflammatory components consistent with roles for the acquired immune system [12].

Roles for T cells in AD

AD pathological studies have long shown evidence for changes in a broad range of immune cells [13], particularly including a high presence of microglia [14]. More recently, genetic and pathological studies indicate a role associated with neurotropic virus, particularly herpes simplex [15,16]. It has been suggested that a function of Aβ peptide is to provide a protective mechanism against infection by herpes virus [17].

T cells in both the periphery and CNS are also implicated in AD, although their roles in neurodegeneration are unknown. Early pathological studies of AD patient brains reported higher numbers of $CD3^+$ T cells in AD patients than healthy age-matched controls [18–21]. The number of hippocampal $CD3^+$T cells was correlated with tau pathology, but not Aβ plaque load [21]. This observation implies that the extravasation of T cells into the brains of AD patients is due to tau deposition, although tau-specific T cell responses have not yet been reported.

AD mouse models that recapitulate Aβ pathology have demonstrated T cell infiltration in the brain. $CD3^+$ T cells localize to the hippocampus of ArcAβ, APP-PS1-dE9, and Tg2576 mice, which display cerebral amyloidosis, but not in E22ΔAβ mice, in which pathology is restricted to intracellular Aβ [22]. While the number of infiltrating T cells is correlated with plaque load, these T cells do not localize on or adjacent to Aβ plaques [22]. Adoptive transfer of nonspecific Tregs into a 3xTg mouse model of AD improved cognition and reduced Aβ deposition, while depletion of Tregs aggravated spatial learning deficits in the same mice [23]. Contradictory to this finding, depletion of Tregs in the 5XFAD mouse model was also followed by reduced Aβ deposition and reversal of cognitive decline [24].

Aβ has been described as one of the antigenic targets of T cells in AD. Mouse models have indicated that protective vs. pathogenic functions of Aβ-specific T cells is determined by their Th subset phenotype, although results are contradictory. On one hand, Aβ-specific Th1 (IFNγ-producing) was shown to impair cognitive function [25], but it has also been shown that IFNγ-producing T cells improves cognitive function [26]. Aβ-specific Th2 have been shown to reverse cognitive impairment [27]. In humans, T cells that proliferate in response to Aβ has been described as significantly higher in AD patients and age-matched controls as compared to young / middle-aged (25-40 years old) adults [28]. The $Aβ_{16-33}$ peptide has been identified as an immunodominant epitope in individuals irrespective of age and disease status [28]. An age-matched control cohort displayed divergent responses, with some showing highly responsive T cells, and others with no reactivity. As AD is the most prevalent neurodegenerative disease, some controls were likely presymptomatic, and it may be necessary to follow individuals longitudinally to determine if Aβ reactivity has potential as a diagnostic marker.

Roles for T cells in PD

In addition to many long-standing reports of sustained microglial activation, particularly in the SN of PD patients, more recent lines of evidence suggest a role for T cells in PD [1••]. Both early and more recent pathology studies found that $CD8^+$ and $CD4^+$T cells were

present at higher levels in the SN of PD brains [29–31], although the antigenic targets were not defined. In a mouse model using viral α-syn overexpression, MHC class $II^{-/-}$ mice were protected from SN neuronal death [32], indicating a role of MHC class II in neuronal death. Moreover, genome-wide association studies (GWAS) associated PD with DRB1*15:01 and DRB5*01:01 HLA class II alleles [33••], although it was not known whether this association might reflect recognition of α-syn epitopes in the context of these alleles.

Human T cells recognize α-synuclein derived peptides in PD patients

To address whether PD is associated with α-syn-specific recognition by T cells, peripheral blood mononuclear cells (PBMCs) from 67 PD and 36 healthy, age-matched controls were screened with potential α-syn peptides [1••]. These peptides included both overlapping 15-mers spanning α-syn and 9-10-mers predicted to bind common HLA class I alleles. This study identified several T cell epitopes, with the majority of α-syn-specific responses directed against two main antigenic regions; one centered around Y39, and the other around phosphorylated-S129 (pS129), a post-translational modification of α-syn found in Lewy bodies. The experiments revealed that the autoimmune responses to Y39 and pS129 were significantly higher in PD compared to age-matched controls. Recently, the increased frequency of α-syn-specific T cells in PD patients was confirmed by an independent study [34]. The α-syn-specific T cell responses were primarily mediated by $CD4^+$ T cells (and some $CD8^+$T cells) secreting IL-5, IFNγ, and to lesser extent IL-10. Some PD-specific α-syn epitopes identified in this study also displayed distinct HLA class II binding characteristics, while one epitope region demonstrated little clear restriction suggesting that it is associated with promiscuous HLA class II binding capacity. In both cases binding to five or more alleles was observed. In particular, the Y39 epitope bound the PD-associated DRB1*15:01 and DRB5*01:01 HLA proteins with high affinity, thus closely mirroring the HLA association reported in the GWAS studies. This was further analyzed by examining whether specific HLA alleles were significantly enriched in the individuals responding to the α-syn epitopes. We found that α-syn responses were significantly associated not only with HLA DRB1*15:01 and DRB5*01:01, but also DQB1*03:04 and A*11:01. Further investigation revealed that the Y39 antigenic region contains nested epitopes with an HLA A*11:01 motif that elicit IFNγ production. Additionally, we showed that HLA DRB1*15:01 expression is associated with a trend towards higher expression compared to DRB1*15:01 controls in individuals with PD. Thus, suggesting that higher expression of DRB1*15:01 could result in more HLAs available to aberrantly interact with α-syn peptides, or that the higher expression of the allele may reflect a general inflammatory state in the individuals with PD.

A recent study identified a region in α-syn with high homology to a region in HSV-1, and that both of these regions stimulated T cell responses in individuals with PD [35•], thus suggesting an environmental role in PD pathogenesis and triggering an autoimmune response [36]. In conclusion, the Y39 epitope binds with high affinity and specificity to DRB1*15:01 and DRB5*01:01, and α-syn responses are associated with DRB1*15:01, which corresponds to the alleles associated with PD in GWAS studies. The data further revealed a minor PD association with DQB1*03:04 and A*11:01. These data establish a crucial link between disease susceptibility and T cell recognition.

A working model for the role of T cells in neurodegenerative disorders

Based on these results, we have suggested a model in which α-syn-specific T cells drive neuronal death in neurodegenerative diseases associated with specific misfolded proteins. $CD4^+$ T cell recognition of antigens presented by APC such as microglia, and by $CD8^+$T cells on neurons, could mediate both direct and indirect neuronal damage. Substantia nigra and locus coeruleus neurons express HLA class I [9••], but there has been no description of HLA class II expression. Importantly, α-syn-epitope specific T cells have been shown to recognize exogenous native antigen (both monomer and fibrils) [1••], demonstrating that T cells can respond to epitopes arising from natural processing by APCs of extracellular native and fibrilized α-syn. Moreover, a recent study has shown that IL-17, a cytokine commonly secreted by $CD4^+$T cells, can cause direct neuronal damage via IL-17-receptors on human IPSC-derived dopaminergic neurons [37•], providing an alternative method to how PD patient derived T cells can direct neurodegeneration. α-Syn may not be the only protein causing an autoimmune response in PD. The α-syn epitopes identified thus far are not immunogenic in 100% of individuals with PD, suggesting that other antigens might exist. For example, Lewy bodies have been known to contain tau protein and, similarly to α-syn, post-translational modifications of tau accumulate with age and/or disease. To investigate antigenicity to tau, we have synthesized tau derived peptides and are in the process of assessing their immune reactivity in individuals with PD.

We speculate that aggregated and misfolded proteins implicated in neurodegenerative disorders, for example α-syn, tau and Aβ, are particularly prone to internalization by microglia and other immune cells with phagocytic and HLA class II processing capacity, thus initiating a cascade of events linked to immune processes (Figure 1).

Outlook for further investigations

The current data implicating α-syn and Aβ epitopes may represent the proverbial tip of the iceberg for characterizing the role of the immune response in neurodegenerative disease. Clearly, much remains to be done. Analysis of reactivity against other additional autoantigens associated with PD, as well as investigation of the potential for T cell autoimmunity in other neurodegenerative diseases such as AD and ALS, is of clear interest. Future research should analyze the relationship between autoimmune reactivity and development of clinical manifestations. More in-depth analysis of antigen-specific T cell subsets in neurodegenerative diseases may provide avenues to limit disease progression. For example, there is limited evidence that IL-10 production is associated with recognition of α-syn epitopes by human T cells from PD patients [1••]. If these cells are distinct from those responsible for inflammatory adaptive responses, it is possible that they might be associated with regulatory functions [38], and their induction is of potential therapeutic interest. We are currently investigating α-syn-specific IL-10 regulatory responses in relation to their potential role in pathogenesis and therapy, performing phenotyping studies to establish which cell type is responsible for IL-10 production, and studying the correlation of IL-5, IFNγ and IL-10 production with the time after clinical disease onset.

It is widely appreciated that these disorders are associated with a protracted prodromal phase, where neurodegeneration precedes the onset of clear symptoms. For PD, by the time of diagnosis, 60-80% of SNpc neurons have already degenerated [39], a situation which bears some similarity to autoimmune disease (i.e., diabetes), where significant inflammation and damage precedes onset of clinical disease [40]. Detection of PD prior to SN neuron loss is a major goal of PD research, and intervening during the prodromal period may delay or prevent SNpc degradation [39]. It is therefore important to investigate whether T cell reactivity is associated with the prodromal phase; it is conceivable that a T cell based assay may identify individuals at risk or in early stages of neurodegeneration. For this purpose, the characterization of the TCR repertoire associated with recognition of α-syn and other antigens in neurodegenerative diseases will likely provide important answers. Identification of antigen-specific T cells in eurodegenerative diseases will help unveil previously unknown mechanisms that cause neurodegeneration, as well as guide the development of biomarkers, diagnostic tools and treatments and thus help affected individuals.

Conclusions

Our data establish a crucial link between T cell recognition and susceptibility to PD, a common neurodegenerative disease. Understanding the role of adaptive immune responses in neurodegenerative diseases may provide novel diagnostic and/or therapeutic strategies. Our current research efforts are aimed at expanding these lines of investigation to other antigens and other neurodegenerative diseases, and to dissecting the role of T cell reactivity in the prodromal phase and disease pathogenesis.

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• of special interest

•• of outstanding interest

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Highlights

- T cells play a role in neurodegenerative diseases
- T cells recognize α-synuclein derived peptides in Parkinson's patients
- T cell recognition and susceptibility to Parkinson's disease is linked
- Understanding autoimmune reactivity may improve diagnosis and treatment options
- The relation between autoimmunity and development of disease should be explored

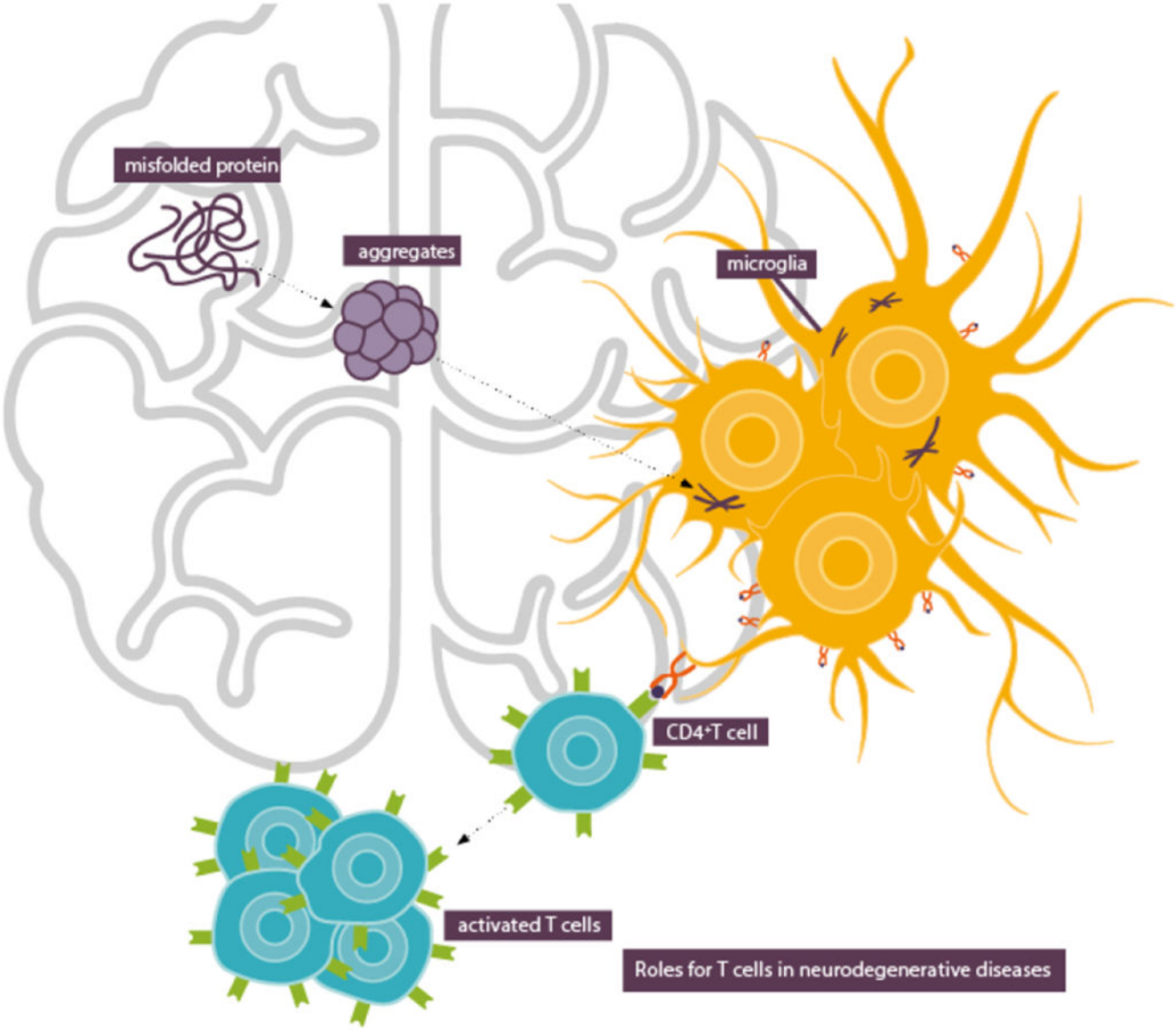

Figure 1.
Aggregated and misfolded proteins are internalized by microglia and other immune cells which leads to T cell activation.