Immune System and Parkinson's Disease

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Citation: Perez A, Guan L, Sutherland K, et al. Immune System and Parkinson's Disease. Arch Med. 2016, 8:2.

Abstract

Parkinson's disease (PD) is the second most common neurodegenerative disease and features many symptoms of motor neuron degeneration including bradykinesia, resting tremor, rigidity, and loss of postural reflexes. Presently there is no cure for PD and treatment methods are focused on addressing clinical symptoms, as the true pathological cause of the disease is still unknown. However, it is interesting to note that aging is the most important risk factor in the development of PD and similarly the immune system drastically changes with increased age. A weakening of the immune system, caused by aging, leads to the inability to metabolize a normal protein in the body, known as alpha synuclein. Toxic aggregation of this protein is linked to PD, and causes the formation of Lewy-bodies and Lewy neurites. These initiate a response from the innate immune system, which leads to a chronic inflammatory response in the CNS. In spite of the unbalanced immune system present in the aged population, methods of immune modulation hold promise in returning the immune system back to its balanced state present in youth. The discovery of a biomarker present in the primitive stages in disease pathophysiology may unlock the key changes which lead to the disparity between the innate and adaptive immune system causing the progression of PD. In this review, we will collectively describe changes in the immune system of PD patients in hope that it will provide insightful information to better understand the etiology of PD.

Keywords: Parkinson's disease, Immune therapy, Immunomodulation, Alpha synuclein, Immunotherapy, Immune modulation

Introduction

Parkinson's disease (PD) was established as a medical condition many years after James Parkinson noted a resemblance in cases amongst his older patients in his 1817 publication "An Essay on the Shaking Palsy" [1]. It is characterized as a progressive neurodegenerative movement disorder that results from the death of dopaminergic neurons in the substantia nigra [2]. Presently, there is no known cure for PD and drugs used to treat it are focused on suppressing symptoms instead of preventing the onset or the progression of the disease. The most common drugs used to treat PD are dopamine or dopamine derivatives such as L-DOPA, which have been found to cause levodopa-induced dyskinesias (LIDs) following chronic treatment [3]. Many other treatments have been developed and applied in the clinical setting including natural products, vaccines, antibody treatments, receptor agonists, and physical treatments but have so far been unsuccessful in preventing or slowing the disease.

Modern medicine is extending the average lifespan of the population making the prevalence of PD increasingly impactful on society. Today PD affects about one million patients in the United States and more than seven million worldwide with a mean age of diagnoses occurring in the seventh decade of life [4]. PD pathology is currently classified as either idiopathic or hereditary, however only 5-10% of PD cases are inherited and attributed to a specific gene mutation [5]. The higher prevalence of PD found in the older population compared to the younger population lends support to the hypothesis that its pathogenesis is correlated with immunosenescence and an aging body.

Patients suffering from PD may begin to display symptoms many years before the disease is clinically diagnosed. Currently there is no pinpoint diagnostic test for PD, therefore diagnoses relies on the clinical detection of two of the four cardinal signs of PD which include resting tremor, bradykinesia, rigidity, and postural imbalance [6]. In addition to the physical symptoms, PD patients

commonly display non-motor symptoms such as depression, lack of motivation, passivity, and dementia [7]. After PD is diagnosed, patients live an average of 15 years before death occurs [8]. The prodromal phase associated with PD can last many years and can be attributed to the slow rate of decline of the immune system with age [9]. Accurate prognosis of PD relies on the discovery of a biomarker present in the immune system attributed to the disease that can be modified to prevent disease pathophysiology.

This review article will explore changes in the immune system of PD patients that lead to an imbalance between the innate and adaptive immune systems in order to hopefully uncover the etiology and pathophysiology of the disease.

The Pathological Markers of PD

The clinical detection of PD in patients lies along a broad spectrum starting from normal to severely impaired motor and non-motor functions. Unfortunately, the presence of motor skill impairments may not be used as appropriate biomarkers due to the significant amount of neurodegeneration already present at this stage in disease pathophysiology [10]. The discovery of an early biomarker will allow patients to receive treatment at the inception of disease progression consequently minimizing dopaminergic neuronal loss and increase the success of therapeutic efforts. The present-day absence of an early defining stage in PD development creates urgency for the identification of specific biomarkers that can be used in studies focused on preventing the development of PD.

One promising method for the detection of a useful biomarker is research on the exposome. The exposome consists of all human environmental exposures from conception onwards [11], and is a biological record of the body's interaction with disease and environmental exposures. Through the completion of the exposome, it will be possible to determine environmental causes that lead to the degradation and deregulation of the immune system occurring with age leading to the discovery of useful biomarkers to identify the PD in its premature stages of progression. Though at this time research is limited in this area, and it will take further studies to fully utilize the exposome with regards to the prognosis of PD.

Currently, the most commonly used pathological marker for PD is the aggregation and misfolding of the endogenous protein α-synuclein, which is efficiently metabolized by the body at the monomeric level and when there is an appropriate balance between innate and adaptive immunity. After the immune system ages and is no longer able to properly metabolize α-synuclein, the protein becomes main component of the toxic aggregates termed Lewy bodies (LBs). These toxic aggregates pose a problem to the declining immune system. As the aggregates continue to grow due to their prion-like nature, they are marked as foreign by the innate immune system leading to an influx of phagocytic cells to the area which are unsuccessful in engulfing and destroying the large oligomers at this stage in disease advancement. The continued inability to metabolize the large toxic aggregates causes a chronic inflammatory process that eventually leads to neuronal death. After cell death occurs, the apoptotic factors released contribute to the further recruitment of inflammatory

elements. Thus, the increase of inflammatory factors and the progression of this immune cascade in PD patients can potentially be used as early biomarkers for disease detection and immune modulation.

One of the hallmarks of PD is the death of dopaminergic neurons (DA). DA neurons have recently been demonstrated to have characteristics of traditional antigen presenting cells (APCs), such as dendritic cells. DA neurons can process foreign ovalbumin (OVA), a 385 amino acid protein that is found in egg whites. This sequence is cleaved to SIINFEKL peptide in vitro and presented by traditional APC, and by major histocompatibility complex class-I (MHC-I). This ability demonstrates the DA's ability to process foreign protein and display derived peptides on the cell surface [12]. Neuronal MHC-I can subsequently trigger immune response and T-cell-mediated cytotoxic attack and degradation.

Red blood cells (RBCs) contain 99% of the α-synuclein present in the blood [13]. In a person with a healthy immune system, once red blood cells reach the end of their lifespan, they lyse and the α-synuclein is released into the blood stream where it becomes ably metabolized. The red blood cell life cycle occurs continuously throughout life and once α-synuclein becomes released into a weak and unbalanced immune system the protein is not sufficiently metabolized, leading to a continual increase in the amount of α-synuclein present in the blood [14,15].

As shown in **Figure 1**, the accumulation of α-synuclein monomers in the blood increases the chances of the protein interacting to form a higher order molecule. The free α-synuclein monomers circulating in the blood that are not metabolized remain undetected by the immune system. Once these monomers bind to other monomers, forming a stable dimer or oligomer of higher order structure, they are recognized as foreign by the immune system and illicit an inflammatory immune response. These interactions between α-synuclein monomeric units lead to the formation of various conformers that have been observed in the brain [16]. Thus, early detection of high concentrations of α-synuclein in the peripheral blood may serve as a potential biomarker of PD before the protein invades and affects the central nervous system.
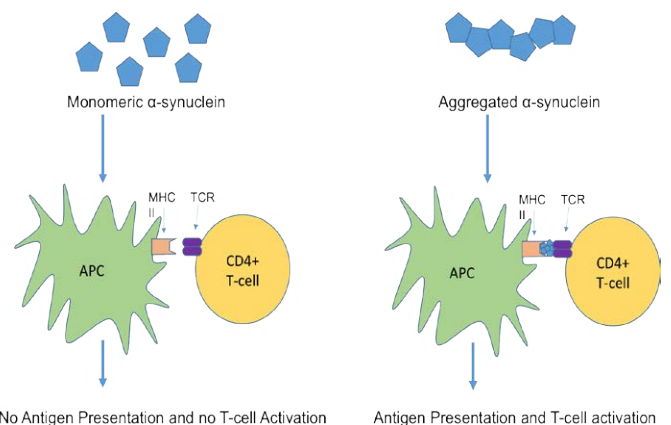

Figure 1 Activation of immune system by α-synuclein aggregates.

As the inflammatory state of the PD br... persists, the blood brain-barrier becomes increasingly permeable, allowing the entry of T-cells. The α-synuclein causes induction of microglial major histocompatibility complex class II (MHCII) and subsequent antigen presentation [17]. We hypothesi... sensitization of T-cells through the course... increase rate of degeneration of dopa... exhibit MHCI presentation of α-synuclein...

The Immune System in P...

The immune system is categorized int... immunity. Innate immunity is present at b... response to defend the body from infectio... immune system, the adaptive immune s... mount a specific immune response ag... Although both the innate and adaptive i... affected by aging, the biggest toll is pla... immune system [19].

The declining of the immune system is considered a normal part of the aging process. Immunosenescence is clearly demonstrated through the involution of the thymus, which plays a major role in the development of T cells in the adaptive immune system and the increased presence of diseases amongst the elderly population [20]. Due to a weakened immune system, the elderly exhibit immunological tolerance through a decreased response to vaccination which leads to the need for vaccines of higher doses in order to elicit an appropriate response from the adaptive immune system [21]. These changes indicate the immune system in older individuals loses its strength through the inability to maintain the critical balance present at younger ages increasing susceptibility to diseases.

A key feature of a healthy immune system is the appropriate recognition between "self" and "non-self" when mounting immune responses. PD patients have demonstrated an increase in heterogeneity of immune responses leading to inappropriate autoimmune reactions towards endocrine insulin and astrocytical S100B [22]. These immune reactions may represent the neurodegenerative processes leading to disease pathology occurring in the brain. The inappropriate responses can also potentially occur against other endogenous proteins related to the disease such as alpha synuclein, leading to a myriad of other immune system alterations.

Changes in the innate immune system

A key change found in the aging innate immune system is a decrease in the amount of dendritic cells [23,24]. Dendritic cells (DC) are involved in capturing and processing foreign antigens, expressing lymphocyte co-stimulatory molecules, and secreting cytokines to elicit an immune response from the adaptive immune system [25]. Studies have found aged DCs to exhibit altered functions such as the impaired ability to induce T cell proliferation [26] and to increase levels of proinflammatory cytokines [27]. The changes made in dendritic cells may clarify the role played by the innate immune system to the overall development of immunosenescence and provide insight on possible immune modulating treatments [23].

microglia are resident macrophages present in the CNS that serve as a neuroprotective medium through the defense against infectious diseases, inflammation, trauma, ischemia, brain tumors, and neurodegeneration [28]. Once presented with ... become activated quickly to eliminate ... n of microglia takes place before any ... ell death takes place so it is used as a ... ronal injury [29]. In PD, an increased ... oglia in the brain is associated with the ... is believed to actually cause an effect ... degeneration by inducing cell death in ... 30]. Once microglia become activated ... -synuclein, they may remain activated ... subsequent stimuli thereby enhancing ... dative stress [31].

... ent of dendritic cells and microglia are ... s) of the innate immune system present on the cell surface. Toll-like receptors function to recognize constituents of invading pathogens, which induces the production of proinflammatory cytokines and activates a response from the antigen-specific adaptive immune system [32]. The activation of the adaptive immune system via TLRs may contribute to the disparity present between the innate and active immune system present in PD patients leading to further disease progression. The role played by TLRs in the inflammatory cascade makes them a potential target as a viable biomarker for the development of future PD treatments.

Changes in the adaptive immune system

Consequential changes occur in the adaptive immune system with age that inhibit the body's ability to maintain the critical balance necessary to maintain a disease-free environment. A notable change occurs to hematopoietic stem cells (HSCs) which function to give rise to all cells present in the blood. Previous research has shown that the phenotypic and functional properties of HSCs change during ontogeny [33]. Due to the defects accumulated by HSCs with age, their population declines because of their reduction in regeneration ability. The modifications to HSCs leads to the subsequent decrease in production of naïve T cells and naive B cells in the bone marrow and thymus contributes to the disruption of balance between the innate and adaptive immune system responsible for keeping the body disease free at younger ages [34]. Due to the decreased population of naïve cells in the older population, the ability of the immune system to recognize new antigens subsequently diminishes [35].

The purpose of immunomodulation in treating PD and other diseases caused by the immune system is to bring the immune system back to its balanced state present in earlier stages of life. By identifying changes occurring in the immune system of PD patients, it would be possible to prevent the disease or stop its progression at an earlier stage. Targeting these changes within the immune system, such as those presented in **Table 1**, may help to slow the neurotoxic environment that is created by over activation and inflammation of the immune system. Parkinson's disease is an age related disorder, and it is possible that a cure may likely be found in a young and healthy immune system.

Table 1 Summary of potential immune targets in PD.

	Role in Immune System	Role in PD
TNFα	Cell signaling protein involved in triggering apoptotic cell death and inflammation	Present in elevated levels in PD patients [36,37]; mediates cell death in a responsive population of DA neurons by activating brain microglia [38,39]; stimulates production of nitrogen oxide lead.
IFN γ	Involved in both innate and adaptive immune system; activates macrophages and causes expression of Class II Major histocompatibility molecules (MHC)	Present in elevated levels in PD patients [40]; involved in death of DA neurons by up regulating microglial activity [40,41].
IL-1β	Pro-inflammatory cytokine; involved in cell proliferation, differentiation, and apoptosis	Present in elevated levels in PD patients [37]; sustained pro-inflammatory levels has toxic effects in the substantia nigra [42]
TGF-β1	Anti-inflammatory cytokine	Conjunction with IL-6 generates high amounts of Th17 causing additional inflammation [43]
IL-6	Pro-inflammatory cytokine; involved in acute phase response	Increased levels correlated with severe depression, fatigue and cognitive difficulties in PD patients [44]; acceleration of muscle catabolism/poor physical performance [45]
IL-10	Anti-inflammatory cytokine; Up regulation of humoral response, Down regulation of cellular response	Aids in protecting against LPS-induced loss of dopaminergic neurons [46]; decreased levels found in aged brain [47]
IL-4	Stimulate differentiation of naïve helper T cells to Th2 cells; Stimulate active B cells	Increased concentrations in PD patients [48]
Dendritic Cells (DCs)	Antigen-presenting cells; link between innate and adaptive immune systems	DC levels decrease as PD symptoms become more severe[49]; Vaccination may be an effective treatment against α-synuclein [50]

Conclusion

The correlation between an aging immune system and Parkinson's disease must not be ignored. As patients continue to age, the immune system gradually undergoes changes that increase the risk of developing PD, and everyone is susceptible as 90-95% of the cases are sporadic. By continuously studying the evolving immune system, we come closer to being able to intervene and restore it to its balanced form present at younger ages. It is crucial to identify and adjust the disparity between the innate and adaptive immune system in order to prevent disease onset and progression. Aiding in this goal would be the discovery of an early biomarker present in the primitive stages of disease development. Also critical in future research is the further role characterization and elucidation of underlying mechanisms of the many immune cells related to disease pathogenesis. The identification of an earlier marker and more in depth information about the contributing immune cells would allow for the combinatorial use of drugs used presently along with methods of immunomodulation to return the immune system to its healthy and balanced state.

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