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## Evidence that Parkinson's disease is partly an Autoimmune Disease

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## **Abstract:**

Parkinson's disease is a neurodegenerative disorder that affects dopaminergic neurons; the symptoms are the result of the gradual degeneration of nerve cells in the portion of the midbrain that controls body movements.

For degenerative diseases like Parkinson's, any insights into its development in the brain could be vitally important in coming up with new ways and approaches for treatment. Several studies have been made to better understand this disease but new series of researches are focusing on the underlying autoimmunity of the disease and whether it plays a role in its progression or not.

For this reason, a new series of studies could form a key piece of the puzzle. They have found the first direct evidence that autoimmunity contributes to Parkinson's disease, by extension raising the prospect of manipulating the body's immune system to slow or even halt its progress.

## **Introduction:**

Parkinson's disease (PD) is a progressive disorder of the nervous system that affects movement. It develops gradually, sometimes starting with a barely noticeable tremor in just one hand. However, while a tremor may be the most well known sign of Parkinson's disease, the disorder also commonly causes stiffness or slowing of movement.<sup>1</sup>

In Parkinson's disease, certain nerve cells (neurons) in the brain gradually break down or die. Many of the symptoms are due to a loss of neurons that produce a chemical messenger in your brain called dopamine. When dopamine levels decrease, it causes abnormal brain activity, leading to signs of Parkinson's disease.<sup>2</sup>

Therefore Parkinson's disease is a neurodegenerative disorder that affects predominately dopamine-producing (“dopaminergic”) neurons in a specific area of the brain called substantia nigra.

Symptoms generally develop slowly over years. The progression of symptoms is often a bit different from one person to another due to the diversity of the disease

The cause remains largely unknown. Although there is no cure, treatment options vary and include medications and surgery. While Parkinson's itself is not fatal, disease complications can be serious.<sup>1</sup>

Autoimmunity is the driving force behind diseases such as rheumatoid arthritis and multiple sclerosis. Normally our body's immune system acts as its protector, tracking down and fighting off foreign invaders like viruses, bacteria or cancer cells. Nevertheless, sometimes the immune system can mistake our own cells for hostile ones, launching an attack on our healthy tissues and organs.

It was believed that dopamine neurons, whose death or impairment plays a central role in Parkinson's, were not vulnerable to such autoimmune attacks. However, a recent study proposed the idea that these neurons actually were susceptible because of proteins that form on the cell surface that serve as a green light for the immune system to recognize and attack foreign invaders.<sup>3</sup>

## **Discussion:**

### **The Role of Dopamine**

The dopamine neurons of the substantia nigra generate dopamine and release that chemical in different areas of the brain. The primary regions of that release are areas of the brain called the *putamen* and the *Caudate nucleus*. The dopamine neurons of the substantia nigra have long projections (or axons) that extend a long way across the brain to the putamen and caudate nucleus, so that dopamine can be released there.

In Parkinson's disease, these 'axon' extensions that project to the putamen and caudate nucleus gradually disappear, as the dopamine neurons of the substantia nigra are lost.<sup>3</sup>

### **Progressive loss of dopamine**

As less and less, dopamine is produced by the neurons affected by Parkinson's disease, far less dopamine is available to bind to the dopamine receptors on the post-synaptic membrane.

Degradation of dopamine neuron is particularly evident in a part of the substantia nigra called the *pars compacta*. As the severity of PD increases, the depletion of dopamine leads to further changes in the basal ganglia pathways, including altered function of other basal ganglia neurotransmitters.<sup>3</sup>

### **Lewy bodies and alpha-synuclein**

Lewy bodies are abnormal aggregates and inclusions of protein that develop inside nerve cells in people with Parkinson's disease. The aggregations usually consist of insoluble fibrillary aggregates containing misfolded proteins. A large number of molecules have been identified in Lewy bodies but a protein called alpha-synuclein is the main component.

Although the function of alpha-synuclein is not well understood, studies suggest that it plays a role in maintaining a supply of synaptic vesicles in presynaptic terminals by clustering synaptic vesicles. It may also help regulate the release of dopamine.<sup>4</sup>

### **Inflammation and immune response**

The trigger of dopaminergic degeneration seems to be multifactorial—affected by both endogenous and environmental elements. Inflammation and immune responses are increasingly being considered as important mediators of dopaminergic degeneration.

Parkinson's begins with abnormal clumping of a protein called alpha-synuclein in the brain. Neighboring dopamine-producing neurons then die, causing tremors and difficulty moving.

The common understanding has been that these neurons die from a toxic reaction to synuclein deposits. However, Parkinson's has been linked to some gene variants that affect how the immune system works, leading to an alternative theory that synuclein causes Parkinson's by triggering the immune system to attack the brain.

An argument against this theory has been that brain cells are safe from immune system attack, because most neurons do not have antigens – the markers immune cells use to recognize a target. However, by studying postmortem brain tissue samples, David Sulzer at Columbia University and his team have discovered that dopamine-producing neurons do display antigens.<sup>4</sup>

These findings suggest Parkinson's may be an autoimmune disorder, in which the immune system mistakenly attacks part of the body.<sup>4</sup>

There have been hints before that the immune system is involved in Parkinson's, but this is the first evidence that it plays a major pathological role.<sup>4</sup>

### **Evidence that Parkinson's disease may be an autoimmune disorder**

Now in a follow-up study, Sulzer and his team have zoomed in on the mechanism behind this high-stakes case of mistaken identity, a damaged protein that accumulates in the brain cells of Parkinson's patients called alpha-synuclein. The team examined blood samples from 67 Parkinson's disease patients and 36 healthy controls after exposing them to fragments of damaged alpha-synuclein, along with other proteins found in the neurons.<sup>5</sup>

This exercise allowed them to see which, if any, of the protein fragments triggered an immune response. They saw little activity in the blood samples in the healthy patients, but the T cells in Parkinson's patients, which are key players in our immune response, got to work and launched a strong attack on the damaged alpha-synuclein.<sup>5</sup>

### **What does the autoimmunity role suggest?**

It remains to be seen whether the immune response to alpha-synuclein is an initial cause of Parkinson's or if it contributes to neuronal death and worsening symptoms after the onset of the disease

These findings, however, could provide a much-needed diagnostic test for Parkinson's disease and could help us to identify individuals at risk or in the early stages of the disease

If abnormal alpha-synuclein begins to accumulate, and the immune system has not seen it before, the protein could be mistaken as a pathogen that needs to be attacked

These findings raise the possibility that an immunotherapy approach could be used to increase the immune system's tolerance for alpha-synuclein, which could help to ameliorate or prevent worsening symptoms in Parkinson's disease patients.

The Sulzer and Sette labs which conducted the research are now analyzing these responses in additional patients, and are working to identify the molecular steps that lead to the autoimmune response in animal and cellular models.<sup>6</sup>

### **Conclusion:**

Parkinson's disease is a progressive disorder of the nervous system that affects movement. A lot of studies have been made to try to fully understand the possibility of an underlying autoimmune role in Parkinson's but now researchers have found the first direct evidence that autoimmunity -- in which the immune system attacks the body's own tissues -- plays a role in Parkinson's disease. These findings raise the possibility that the death of neurons in Parkinson's could be prevented by therapies that dampen the immune response

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