Parkinson’s Disease: Neurobiology and Therapeutic Strategies

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Parkinson’s Disease (PD) is the second most common neurodegenerative disease after Alzheimer’s Disease. Diagnosis is primarily clinical and is based on the presence of asymmetric or unilateral resting tremor, bradykinesia and rigidity. These motor features are predominantly the result of the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and loss of striatal inhibition. Accumulation of α-synuclein in intraneuronal Lewy bodies and neuritis is a pathological hallmark of PD. Neurodegeneration also develops in a non-motor feature that include cognitive impairment, sleep disturbances and autonomic dysfunction. The clinical diagnosis of PD may be preceded for several years by prodromal features that include hypomobility, rapid eye movement sleep behaviour disorder, depression and constipation. The known causes of PD include several gene mutations of proteins including in alpha-syn, LRRK2, parkin and PINK1 and glucocerebrosidase (GBA1).

Environmental and Genetic Factors

The Genes and Proteins Involved in Parkinson’s Disease

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Current and Emerging Treatments for PD

The contribution of the gut microbiota to PD pathogenesis has attracted

Modification in PD include the use of GLP-1 agonists e.g. exenatide, LRRK2

Potential Neuroprotective Interventions

Fig. 1. PD is a neurodegenerative disease characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and subsequent loss of striatal inhibition. The SNpc is disrupted in PD pathogenesis. Simply put, dopaminergic neurons in the SNpc project to GABAergic neurons in the GABAergic neurons in the ventral tegmental area (VTA) and substantia nigra pars reticulata (SNpr). In PD, along with the loss of dopaminergic neurons in the SNpc, the glutamatergic (Glu) neurons in the subthalamic nucleus (STN) have increased activity. The increased activity in the STN is projected to the GABAergic (GABA) neurons in the globus pallidum interna (GPi) with subsequent inhibition of the thalamus and its projections to the cortex.

Disease Stages and Potential Therapeutic Strategies

The bowel...bacterial microbiota that host the gut. These bacteria promote the absorption of nutrients, synthesis of vitamins, and production of short-chain fatty acids. The microbiota also affects the immune system and modulates the host’s response to infections. In the context of PD, the gut microbiota may contribute to disease progression by promoting the accumulation of α-synuclein, a key pathological marker of PD.

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References

Note: This paper presents a general overview and should be considered as a preliminary comprehensive review. The details should be confirmed through specific research studies and clinical trials.

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- α-synuclein in intraneuronal Lewy bodies and neurites is a pathological hallmark of PD. Neurodegeneration also develops in non-dopaminergic pathways and results in a series of non-motor features that include cognitive impairment, sleep disorders and autonomic dysfunction.

- The main motor features of PD are the consequence of loss of dopaminergic pathways, specifically the dopaminergic neurons in the substantia nigra pars compacta (SNpc) and loss of striatal innervation. Accumulation of α-synuclein is predominantly turned over by chaperone expression.

- Neurodegeneration also develops in non-dopaminergic pathways and results in a series of non-motor features that include cognitive impairment, sleep disorders and autonomic dysfunction.

- Disease Stages and Potential Therapeutic Strategies

  - **Dysfunction:** Protein dysaggregation promoters, mitochondrial enhancers
  - **Promotion of compensation:** LRRK2 inhibitors and GBA modulators

- Pathological features associated with PD include neurofibrillary tangles, Lewy bodies, α-synuclein inclusions, mitochondrial and lysosomal dysfunction, and the involvement of α-synuclein metabolism in PD.

- The formation of α-synuclein toxic oligomers and their progression 1-5% (up to 44% in Ashkenazi Jewish) contribute to disease modification in PD. Additionally, the formation of LRRK2 in autophagy add further credence to the importance of lysosomal dysfunction in PD.

- The association of GBA1 mutations, and the involvement of α-synuclein metabolism in PD, as shown below. Additional strategies for disease modification in PD include the use of GLP-1 agonists e.g. exenatide, therapeutic strategies have been proposed to reduce the effects of aberrant inter-neuronal propagation and enhancement of aggregate formation has been observed in PD, suggesting a template for further misfolding e.g. GBA1 activators or chaperones.

- The complex direct and indirect pathways of the basal ganglia are disrupted in PD pathogenesis. Simply put, dopaminergic neurons in the SNpc project to GABA-enk neurons in the globus pallidus (GPe) and GABA-GABA enkephalinergic feedback is disrupted in PD. The snr of the basal ganglia is disrupted in PD.

- The substantia nigra pars reticulata (SNRt) affects the control of movement, and the substantia nigra pars compacta (SNpc) is the dopaminergic cell body of origin of the nigrostriatal pathway. The basal ganglia regulate movement, and parkinsonian features are reversed by disease-modifying strategies that improve dopaminergic function.