Pathophysiology of Parkinson’s Disease

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PARkinson’s Disease

0.5-1.5 MILLION PEOPLE ~50,000 USA new cases are reported annually

Treatments: Drug therapy and deep-brain stimulation to alleviate symptoms, but not causes.

Appears to be slightly more common in men than women

Expectation of a doubling of Parkinson’s patients and costs by 2040

Average age of onset: 60 yo
Onset as early as 2 yo

Both prevalence and incidence increase with advancing age

Cost exceeds $14.4 BILLION each year

~6 MILLION PEOPLE Worldwide

~6 MILLION PEOPLE Worldwide
Hallmark Neuropathology of Parkinson’s Disease

Dauer & Przedborski, Neuron 2003 Review PMID: 12971891


C. Lewy Body

Synuclein
Ubiquitin

A. Normal

B. Parkinson’s Disease

Caudate
Nigrostriatal pathway
SNpc
Parkinson’s disease is more than a Movement Disorder – Braak Staging

https://en.wikipedia.org/wiki/Braak_staging

**Figure 6: Synuclein-immunoreactive Lewy pathology in the PD spinal cord, coeliac ganglion and gastrointestinal tract.**

- **a** | IML with affected preganglionic sympathetic neurons. The dorsal nucleus (pale round area at upper right) is virtually uninvolved.
- **b** | Lewy bodies and Lewy neurites are widespread in nerve cells of the coeliac ganglion (postganglionic sympathetic neurons), shown here from a case at stage 6 of PD pathology. Scale bars in a and b, 200 μm.
- **c** | Auerbach’s plexus of the stomach from an asymptomatic individual at stage 3 of PD pathology. Aggregates are seen in axons of the fibre bundles that connect individual ganglia.
PARkinson’s Disease Is More Than A Movement Disorder

Intracytoplasmic inclusions termed Lewy bodies containing α-synuclein. Substantia nigra not first site of injury in PD, Lewy neurites found in olfactory bulb & autonomic nervous system.

- REM Sleep BD
- Anxiety
- Depression
- Dementia

Hyposmia

Heart Rate Variability

Widespread neuropathology through multiple neuronal systems.

Constipation

Severity progresses over time

- Stooped posture
- Rigid limbs, Reduced facial expressions
- Speech impairments
- Slow movement (bradykinesia)
- Inability to move (akinesia)
- Postural instability, loss of balance
- Sexual difficulties
- Shuffling gait

Often, the first diagnosed symptom of Parkinson’s disease is tremor (trembling or shaking) of a limb.
LAG3 is required for pathologic α-Syn transmission and cell death

LAG3 is required for α-Syn PFF mediated neurodegeneration of dopamine neurons *in vivo*
Pathways of Neurodegeneration in PARkinson’s Disease

NLY01 blocks α-Syn PFF loss of Dopamine Neurons and Behavioral Deficits

A

B

C

D

E

SNpc of Ventral midbrain
Pathways of Neurodegeneration in PARkinson’s Disease

Key players in neuronal death – past and future
PAR Signaling

PARthanatosis (PARP-1-Dependent Cell Death)

- PNAS, 103: 18314-18319 (2006)
- PNAS 111:10209-14 (2014)
- Science Oct 7;354(6308) (2016)
α-Syn PFF-induced dopaminergic deficits are reduced by deletion of PARP-1 or the PARP inhibitor, ABT-888.
PAR accelerates α-Syn fibrillization

A

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B

Normalized ThT fluorescence

C

Oligomers

WB: α-Syn

Relative oligomers level

Time (h): 0 4 24 36 72

PAR 0.2 1 5 20 (nM)

α-syn

+ + + + +

PAR 0.2 1 5 20 (nM)

ns ** *
PAR binding to α-Syn generates a PAR-PFF α-Syn strain that accelerates dopaminergic toxicity in vivo.
Increase of PAR levels in the CSF of patients with PARkinson’s Disease

A

B

C

D

E

F

G

H
Pathways of Neurodegeneration in Parkinson’s Disease

- **α-syn**: Aggregation, Mutations, LAG3, Oxidative Stress, Immune System Activation
- **TNF-α**, IL-1α, C1q
- **A1 activated Astrocytes**
- **Cell Death**
- **Mitochondrial Dysfunction**
- **PARP1**, AIMP2, PARIS, PGC-1α, NRF-1
- **AIF**, MIF
- **PARK**
- **c-Abl**, P-Y143, P-Y39
- **DNA Damage**
- **Age**, Nitritative Oxidative Stress, Cell to Cell Transmission
Pathways of Neurodegeneration in PARKinson’s Disease and Therapies

- **PARkinson’s Disease**
  - Age
  - Nitrative Oxidative Stress
  - Cell to Cell Transmission

- **α-syn**
  - Aggregation
  - Mutations

- **Cell to Cell Transmission**
  - LAG3
  - LAG3 Inhibitors

- **Mitochondrial Dysfunction**
  - DNA Damage
  - PARP1
  - AIMP2
  - Nitrative Oxidative Stress

- **Inhibitors**
  - Inhibitors of Microglia Activation
  - PARP Inhibitors
  - AIF
  - MIF Inhibitors

- **TNF-α**
  - IL-1α
  - C1q

- **Cell Death**
  - A1 activated Astrocytes
  - PGC-1α
  - NRF-1

- **Parkin**
  - P-Y143

- **c-Abl**
  - P-Y39

- **MIF**
  - Cell Death
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