α-Synuclein misfolding and axon degeneration as key pathogenic events in Parkinson’s Disease

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Typical Pathology

-Loss of dopaminergic neurons in substantia nigra
Substantia nigra (SNC) neurons innervate putamen and caudate of striatum
Pathological hallmark of Parkinson’s, the Lewy body, contains $\alpha$-synuclein

(Pigmented midbrain dopaminergic neurons)

(Spillantini, Nature, 1997)
α-Synuclein misfolding and aggregation in Parkinson’s disease

Normal function (synaptic vesicle release)
consequences of $\alpha$-Synuclein misfolding and aggregation in Parkinson’s disease

- Increased exposure to toxins
- Increased concentration of the protein

Pathogenic versions found in synucleinopathies
PD is progressive
α-Synuclein species ‘move’ through the brain in a predictable manner
Prion-like transmission?

(Braak et al. 2004)
What is/are mechanism(s) underlying the spread of synuclein pathology in Parkinson’s disease?
The structure of a Neuron:

- Dendrites
- Stimulus
- Nucleus
- Axon hillock
- Cell body
- Presynaptic cell
- Axon
- Synapse
- Neurotransmitter
- Postsynaptic cell
- Synaptic terminals
Possible mechanisms underlying the spread of synuclein pathology and α-syn aggregation in Parkinson’s disease

Brain structure 1

Brain structure 2

Legend:
- Soluble α-syn
- Fibrils α-syn
- Proteosome
- Vesicle
- Lysosome
- Exosome
- Multivesicular body
- Neuron debris
- Uptake or release
- Cell death
- Activated microglia clearing cell debris
- Dying neuron
- Cell-to-cell transfer
- Defect in clearance mechanisms
- Misfolding / aggregation
- Release
- Uptake
- Clearance
- Defect in clearance
- Accumulation of α-syn
- Anterograde transport
- Uptake
- Migration
- Neuron 1
- Neuron 2
- Resting microglia
- Activated microglia clearing extracellular α-syn
“Seeding” α-Synuclein pathology in human cells

αSyn-Myc fibrils (exogenous)  αSyn (endogenous)  ‘Lewy body’

Luk et al. Virginia Lee (2009). PNAS
The propagation of human α-synuclein from host tissue to transplanted dopaminergic neurons

frequent transfer of α-synuclein from a rat brain engineered to overexpress human α-synuclein to grafted dopaminergic neurons

Transferred human α-synuclein seeds the aggregation of rat α-synuclein in the recipient cell.

Seeding of aggregation of endogenous α-synuclein in the recipient neuron by the transferred a-synuclein.

α-Synuclein exhibits Prion strain-like properties
What is/are mechanism(s) underlying the death of neurons in Parkinson’s disease?
The subcellular structure of the neuron
α-synuclein: multiple sites of toxicity

- Mitochondria toxicity
  - Impaired energy production
  - Apoptosis induction

- Decreased Synaptic vesicle release

- Blocked ER-Golgi transport
  - ER stress and Golgi fragmentation

- Accumulation of CMA substrates?
  - Proteasome impairment
The mitochondria
Effects of α-synuclein on mitochondria

- α-Synuclein
- Cardiolipin
- Complex I
- Autophagic vacuole

- Fragmentation
- Mitophagy
- Neuronal death
- ↓ Δψₘ
- ↑ ROS

- Outer membrane
- Inner membrane

- PINK1
- Parkin

- Neuronal death
The synapse

Trafficking pathways in the nerve terminal. Synaptic vesicles are filled with neurotransmitter and stored in the cytoplasm. Active vesicles are translocated to release sites in the active zone where they dock. Priming involves all steps required to acquire release readiness of the exocytotic complex. Although usually assumed to occur after docking, priming and even triggering may precede docking during sustained activity, resulting in immediate fusion of an arriving vesicle. After exocytosis, the vesicle proteins probably remain clustered and are then retrieved by endocytosis. Despite some lingering controversies, consensus is emerging that retrieval is generally mediated by clathrin-mediated endocytosis. After clathrin uncoating, synaptic vesicles are regenerated within the nerve terminal, probably involving passage through an endosomal intermediate. Actively recycling vesicles are in slow exchange with the reserve pool.
Effects of α-synuclein on synapse integrity and calcium homeostasis
What is the sequence of the pathogenic events leading to the death of neurons in Parkinson’s disease?
Pathological evidence for axonopathy in PD
Spinal cord axonopathy in PD

Cardiac axonopathy in PD

Abnormal asynuclein detected in axons of epicardial nerve fibers before cell bodies of stellate ganglia suggesting a centripetal disease process.

Intestinal axonopathy in PD

Parasympathetic ganglia of esophagus and stomach have Lewy-related pathology in PD

Braak H and Del Tredici K 2008

Braak H and Del Tredici K. Neurology 2008;70:1916-1925
Salivary gland axonopathy in PD

Axonopathy in submandibular glands in PD

Skin axonopathy in PD

Autopsy series: 20 of 85 (24%)
Clinical PD series: 2 of 20 (10%)

α-Synuclein

Nigrostriatal degeneration in PD

Disproportionate striatal terminal loss to S.nigra neuronal loss suggests a dying back axonopathy

Neuron 2003;39:889-909
Striatal terminal loss and nigral neuronal loss at autopsy

Presynaptic pathology

Routine α-synuclein immunohistochemistry

PET blot- abnormal insoluble α-synuclein

Pervasive presynaptic (axon terminal) α-synuclein micro-aggregates in cerebral cortex correlate with dementia

Kramer ML and Schuluz-Schaeffer WJ. J Neurosci 2007; 27:1405-1410
Trafficking pathways in the nerve terminal. Synaptic vesicles are filled with neurotransmitter and stored in the cytoplasm. Active vesicles are translocated to release sites in the active zone where they dock. Priming involves all steps required to acquire release readiness of the exocytotic complex. Although usually assumed to occur after docking, priming and even triggering may precede docking during sustained activity, resulting in immediate fusion of an arriving vesicle. After exocytosis, the vesicle proteins probably remain clustered and are then retrieved by endocytosis. Despite some lingering controversies, consensus is emerging that retrieval is generally mediated by clathrin-mediated endocytosis. After clathrin uncoating, synaptic vesicles are regenerated within the nerve terminal, probably involving passage through an endosomal intermediate. Actively recycling vesicles are in slow exchange with the reserve pool.
Overexpression of α-Synuclein Inhibits Synaptic Vesicle Exocytosis

α-Synuclein Overexpression in Transgenic Mice Inhibits Synaptic Transmission

Field excitatory postsynaptic potentials From hippocampal slices
Overexpression of α-Synuclein Inhibits Synaptic Vesicle Reclustering after Endocytosis