The Pathogenesis of Parkinson’s Disease

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Autosomal Recessive Parkinson’s Disease

early onset (by late 20s)
mild symptoms, slow progression
prominent freezing, hyperreflexia and foot dystonia
improvement after sleep
no Lewy bodies by usual stains
mutations found in diverse families

inherited forms of PD

| PARK1 | dominant | α-synuclein | presynaptic protein |
| PARK2 | recessive | parkin | E3 ubiquitin ligase |
| PARK3 | dominant | 2p13 | ? |
| PARK4 | dominant | α-synuclein | triphosphorylation |
| PARK5 | dominant | UCHL1 | ubiquitin C-terminal hydrolase |
| PARK6 | recessive | PINK1 | mitochondrial kinase |
| PARK7 | recessive | DJ-1 | chaperone? |
| PARK8 | dominant | LRRK2 | leucine-rich repeat kinase |
| PARK9 | recessive | ATP13A2 | P-type lysosomal hydrolase |
| PARK13 | dominant | HTRA2 | serine protease |

parkin is an E3 ubiquitin ligase

?role in protein turnover?
--several proteins identified
but none accumulate in patients, KO mice
and no Lewy bodies in recessive PD!
?another role for ubiquitination?
other autosomal recessive forms of PD

DJ-1 (PARK7) rare
?
protease/?chaperone
protects against oxidative stress

PINK1 (PARK6)
mitochondrial ser/thr kinase

mouse knockouts of parkin, DJ-1, PINK1 have little phenotype

mitochondrial defects
PINK1 → ? → parkin

depolarization with CCCP recruits parkin to mitochondria

(Narendra et al., 2008)

depolarization of mitochondria
and parkin over-expression
--lead to loss of mitochondria
(and increase in lysosomes)
--parkin promotes autophagy of mitochondria

(Narendra et al., 2008)
dominant forms of PD

<table>
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<tr>
<th>PARK</th>
<th>Form</th>
<th>Mutations</th>
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Polymorphisms in synuclein a risk factor for idiopathic PD.
Gaucher’s disease turns out to be a major risk factor (OR~6).

Synucleinopathies
probably general role in PD
a major component of Lewy bodies
even without mutations
extensive deposition
in dystrophic neurites and Lewy bodies

triplication of wild type α-synuclein also causes PD!
deposits in diffuse Lewy Body Dementia,
throughout brain

Multiple System Atrophy is another synucleinopathy
α-synuclein occurs in glial cell inclusions
(PSP, CBGD tauopathies)

but synuclein widely expressed
--so why mainly deposited in dopamine neurons in PD?
Prion-like spread

Braak staging: enteric nervous system to caudal brainstem
Lewy bodies found in some fetal transplants
injection of Lewy bodies or recombinant synuclein fibrils accelerates disease in transgenic mice
mouse fibrils result in spread after injection into wt mice
dopamine neuron loss, behavioral defects
--proof of principle
?significance for idiopathic disorder?
uni- versus multicentric onset

preformed mouse fibrils injected into striatum

lesions in cortex
midbrain, amygdala
--spread between cells:
?monosynaptic
?or more
reduced dopamine
reduced dopamine cells
impaired motor skills

(Luk et al., 2012)
how does synuclein cause PD?

is role in toxicity related to its normal function?

aggregation
forms amyloid (β-sheet)

membrane interaction
normally localizes to nerve terminal
binds to membrane (α-helical)
very weak binding to synaptic vesicles

neural activity disperses α-synuclein at SV fusion

physiological role: unknown

effect of knock-outs controversial

absent from yeast, worms, flies
   --not essential for transmitter release

?modulator set to low baseline level of activity?

binds to artificial membranes with acidic phospholipids
   --not to native membranes (SVs)

paradox: how does synuclein localize to synapses
   despite low affinity interaction?

what does synuclein do to synaptic transmission?

- -knockouts not initially reported to affect transmitter release

AND synuclein actually rescues degeneration!!!

due to loss of cysteine string protein (chaperone)
   --csp a chaperone, refolds proteins involved in release
   --csp not required for transmitter release, initially
   --csp KO shows degeneration after several weeks

is synuclein another chaperone?

- -looked at effects of over-expression
no effect on reporter
no effect on endocytosis
exocytosis impaired

synuclein over-expression 2-3-fold inhibits SV exocytosis

imaging

no effect on reporter
no effect on endocytosis
exocytosis impaired

recording

C-terminus not required
N-terminus is required:
membrane-binding

reserve pool

recycling pool

readily releasable pool

SVs less dense
same number
further from active zone

C-terminus not required
N-terminus is required:
membrane-binding

SVs less dense
same number
further from active zone
α-syn over-expression (Hela cells): mitoGFP

- No defect

- Mitochondria still fragmented in absence of Drp1
**Conclusions**
physiological defect precedes pathology
probably involves a gain in normal function

synuclein can bind to and fragment mitochondria
independent of usual fission machinery
direct interaction
correlates with toxicity

synuclein bends membranes
~other BAR domain proteins (endocytosis)
related role in SV exocytosis?

**Questions**
how does synuclein inhibit release?
what makes synuclein increase
under normal circumstances?

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