Transmission of Misfolded Proteins in Neurodegenerative Disorders: A Common Mechanism of Disease Progression

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Aβ plaques

Tau tangles

α-syn Lewy bodies

TDP-43 inclusions

Stereotypically Spreading of Disease Pathology as Shared Pathogenic Mechanism Among Age-related Neurodegenerative Diseases

Jucker and Walker, 2013
A Large Number of Neurodegenerative Diseases Contain Tau Pathology

- Alzheimer’s disease
- Dementia pugilistica
- Down syndrome
- Prion diseases
- Amyotrophic lateral sclerosis/parkinsonism-dementia complex
- Argyophilic grain dementia
- **Corticobasal degeneration (CBD)**
- Diffuse neurofibrillary tangles with calcification
- **Frontotemporal dementia/parkinsonism linked to chromosome-17 (FTDP-17)**
- Hallervorden-Spatz disease
- Nieman-Pick disease type C
- **Pick’s disease**
- **Progressive supranuclear palsy (PSP)**
- Subacute sclerosing panencephalitis
- Tangle-predominant Alzheimer’s disease
Major Neurodegenerative Diseases with α-Synuclein Pathology

- Parkinson’s disease
- Parkinson’s disease with dementia
- Dementia with Lewy bodies
- Multisystem atrophy
- Alzheimer’s disease
→ **The Transmission Hypothesis:** Can misfolded neurodegenerative disease proteins initiate and induce the cell-to-cell spread of pathology in mouse models?

→ **The Strain Hypothesis:** Do pathological strains exist in neurodegenerative disease proteinopathies that could potentially explain clinical diversity?
Inoculation of Synthetic Mouse α-Syn PFFs into the Dorsal Striatum of Non-transgenic Mice
Intrastriatal injection of mouse α-Syn PFFs in Wildtype Mice Recruit Endogenous α-Syn to form LBs and LNs

Luk et al., Science, 2012
α-Syn pathology in SNpc leads to a progressive loss of DA neurons
SNpc α-Syn Pathology Leads to Impaired Balance and Motor Co-ordination
Intracerebral injections of AD-tau induces more abundant tau pathology than synthetic tau PFFs in non-Tg mice

Guo et al., JEM, 2016
Cell-to-Cell Transmission of Tau Pathology throughout the Neuroanatomical Connectome of Wildtype Mice
Formation of de-novo TDP-43 pathology in CaMKIIa-TDP-43\textsubscript{NLSm} mice injected with FTLD-TDP-43 extracts

Porta et al., Nat Comm 2018
TDP-43 pathology spreading to rostral deep brain nuclei and white matter tracts over time post-injection

Porta et al., Nat Comm. 2018
Summary of Misfolded Neurodegenerative Disease Protein Transmission

- α-Syn PFFs initiate conversion of endogenous α-Syn and their accumulation into Lewy-body and Lewy neurite-like inclusions in animal models.
- α-Syn inclusions drives the selective loss of SNpc DA neurons, resulting in behavioral impairments reminiscent of human PD.
- AD-tau but not synthetic tau fibrils induce neurofibrillary tangle-like pathology in wildtype mice.
- FTLD-TDP enriched lysates induce the formation and propagation of TDP-43 pathology in TDP-43 transgenic mice.
Working Hypotheses

→ **The Transmission Hypothesis:** Can the spread of disease pathology be mediated by misfolded neurodegenerative disease proteins in mouse models?

→ **The Strain Hypothesis:** Do pathological strains exist in neurodegenerative disease proteinopathies that could potentially explain clinical diversity?
Classification of FTLD-TDP based on genetic, clinical correlations and pTDP-43 distribution

<table>
<thead>
<tr>
<th>Molecular class</th>
<th>Pathological subtype*</th>
<th>Associated genes</th>
<th>Clinical phenotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTLD-TDP</td>
<td>(TARDBP)</td>
<td></td>
<td>bvFTD</td>
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<tr>
<td>Type A</td>
<td>GRN</td>
<td></td>
<td>(+)</td>
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<tr>
<td>Type B</td>
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</tr>
<tr>
<td>Type C</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Type D</td>
<td>VCP</td>
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</tbody>
</table>

Modified from Riedl et al., 2014

Cortical Pathology

- A: Many NCI
  - Many short DN
  - Predominantly layer 2
- B: Moderate NCI
  - Few DN
  - All layers
- C: Many long DN
  - Few NCI
  - Predominantly layer 2
- D: Many short DN
  - Many lentiform NII
  - Few NCI
  - All layers

Tau Pathology In CBD, PSP, AD & Related Tauopathies

NFT

Corticobasal Bodies

Globose NFT (PSP)

Pick bodies

Insoluble

Dephos.

72 kDa

68 kDa

64 kDa

60 kDa

AD

FTDP-17

(V337M, R406W)

CBD

FTDP-17

(P301L)

PJD

FTDP-17

(K287T, G396R)

FTDP-17

(N279K, L284L,
N290L, S305N/S,
Intronic mutations)

Soluble

4R/2N

3R/2N

4R/1N

3R/1N

4R/0N

3R/0N

Astrocytic Plaque

Tufted Astrocyte

Astrocytic Inclusion

Neurodegenerative Tauopathies

Human tau strains have different seeding potencies in non-Tg mice

HP/Ctx, 3 months post-injection, IHC for AT8 (pS202/T205)

AD case 1 (1ug/site) n=3
CBD case 1 (1ug/site) n=4
PSP case 1 (0.7ug/site) n=4

One-way ANOVA with Tukey post-hoc (*p<0.05, **p<0.01, ***p<0.001)

Narasimhan et al., J. Neurosci, 2017
CBD-tau, PSP-tau but not AD-tau induced glia tau pathology, recapitulating the human neuropathology

3 months post-injection
CBD case 1 (1ug/site) n=4
PSP case 1 (0.7ug/site) n=4

Injection of AD-Tau into Aβ-bearing mice to generate a AD mouse model with Aβ plaques and neurofibrillary tangles.

He et al., Nat Med, 2018
Tau aggregates are present in the dystrophic neurites surrounding Aβ plaques at very early seeding stages.
Neuritic plaque formation precedes and might even initiate NFT formation

He et al., *Nat. Med.*, 2018
Synucleinopathies

- PD
  - Without dementia: Younger onset, purer LB pathologies, longer onset to dementia, longer disease duration
  - With dementia
- DLB
  - Low NFTs: Older onset, more frequent co-morbid AD pathologies, shorter onset to dementia, more malignant disease course
  - Abundant NFTs
- cLB (Syn)
  - Multiple system atrophy
  - α-syn inclusions predominantly in oligodendrocytes

Can Unique α-Syn Strains from Synucleinopathy Brains be Demonstrated?

Giasson and Lee, 2003
Generation of different strains of α-syn preformed fibrils (PFFs) with distinct seeding properties

Non-Tg neurons (18 d post-transduction)

<table>
<thead>
<tr>
<th>Strain A</th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
<th>P4-P5</th>
<th>P6-P7</th>
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<tbody>
<tr>
<td></td>
<td>(p-α-Syn)</td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>(p-Tau)</td>
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<td></td>
<td>merge</td>
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</table>

P1: de novo Strain A

P6-P7: Strain B

1% Triton-extracted

Guo et al., Cell, 2013
Syn7015 differentiates between LBs and GCIIs in MSA

<table>
<thead>
<tr>
<th>AutopsyID</th>
<th>npDx1</th>
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<td>2008-182</td>
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<tr>
<td>2006-072</td>
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<td>2008-208</td>
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<td>PD/D</td>
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<td>PD/D</td>
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<tr>
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<td>2010-195</td>
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<tr>
<td>2012-181</td>
<td>MSA-P</td>
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</table>
Pathological α-Syn in GCIs and LBs have very distinct conformational and biochemical properties.
GCI-α-Syn is ~1000 fold more potent than LB-α-syn to induce α-syn pathology in primary oligodendrocyte cultures

Peng et al., Nature, 2018
GCI-α-Syn is also ~1000 fold more potent than LB-α-syn to induce α-syn pathology in primary neuronal cultures and QBI cells.
Passage α-syn PFFs in oligodendrocytes but not in neurons or QBI cells could increase its potency.

Intracellular milieu of oligodendrocytes converts α-Syn PFFs to GCI-α-Syn strain.
Once GCI-α-Syn is generated, passage in primary neurons could maintain its high potency.

Peng et al., Nature, 2018
Summary of MSA and PD/PDD brain-derived strains

- GCI-α-Syn and LB-α-Syn define distinct pathological α-Syn strains found in MSA and PD/PDD/DLB brains
- GCI-α-Syn is 1,000-fold more potent than LB-α-Syn in seeding α-Syn aggregation.
- The seeding properties of GCI-α-Syn and LB-α-Syn show no cell type preference.
- Intracellular oligodendrocyte environment converts misfolded α-Syn into a GCI-like strain.
- Neuron environment cannot convert GCI-α-Syn to a LB-like strain.
Conclusions

• Brain-derived tau aggregates from tauopathy brains induce progressive cell type-specific cell-to-cell spread of tau tangles in wildtype and Aβ plaque-bearing mice that recapitulate their human disease counterparts.

• Brain-derived α-Syn aggregates from synucleinopathy brains also induce progressive cell type specific cell-to-cell spread of LB and GCI pathology in wildtype mice recapitulating PD/PDD/DLB and MSA respectively.

• Brain-derived TDP-43 aggregates from FTLD-TDP brains induce progressive spread of TDP-43 aggregates in transgenic mice expressing TDP-43-NLS.

• Transmission of neurodegenerative disease protein strains represent a common mechanism of disease progression and pathogenesis in neurodegenerative diseases.
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