Common Themes in the Pathogenesis of Alzheimer’s Disease, Parkinson’s Disease, and Multiple System Atrophy

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Neurodegenerative Diseases

- A group of neurological disorders characterized by the progressive loss of neurons in the brain and/or spinal cord
  - Alzheimer’s Disease
  - Parkinson’s Disease
  - Multiple System Atrophy
Alzheimer’s Disease

• Clinical characteristics: Memory, language, visuospatial skills, insight and executive function all decline
  • Also see neuropsychiatric symptoms
  • All symptoms progress over time

• Diagnosis
  • Definitive diagnosis requires histopathologic examination
  • Usually done via clinical criteria

• Current treatments offer minimal benefits
  • Cholinesterase inhibitors
  • Memantine (NMDA receptor antagonist)
  • Symptomatic treatments: Anti-psychotics
Alzheimer’s Disease - Pathogenesis

• Amyloid beta
  • Misfolded proteins form extracellular plaques
  • Misfolded oligomers can induce other amyloid beta molecules to misfold, leading to a chain reaction

• Tau
  • Hyperphosphorylated tau protein assembles into intracellular tangles
  • Individual tau fibrils can seed the development of tangles
Prion Proteins

- Prions: Infectious agents composed of protein in a misfolded form
  - Propagate by transmitting the misfolded state to properly folded proteins

![Diagram of prion replication](http://www.jci.org/articles/view/22438/figure/1)
Prion Proteins

• Prions: Infectious agents composed of protein in a misfolded form
  • Propagate by transmitting the misfolded state to properly folded proteins

• Prion diseases: Transmissible Spongiform Encephalopathies
  • Untreatable and fatal
  • Ex.) Creutzfeld-Jakob Disease
Parkinson’s Disease

- Clinical characteristics: Resting tremor, bradykinesia, rigidity, postural instability, cognitive dysfunction, mood disorders
  - Most symptoms worsen over time

- Current treatments
  - Levodopa
  - Deep brain stimulation

http://biomed.brown.edu/Courses/Bi108/Bi108_2008_Groups/group07/DBSsrc-wiredblod.jpg
PD – Pathogenesis and Pathology

- Dopaminergic neuron depletion in substantia nigra
- Pathologic hallmark – Lewy Bodies
  - Contain aggregated and insoluble alpha-synuclein

Multiple System Atrophy

- Clinical characteristics: Parkinsonism (bradykinesia, rigidity), autonomic failure, cerebellar ataxia

- Current treatments
  - None
  - Parkinsonism does not respond to Levodopa treatment
MSA– Pathogenesis and Pathology

• Cause and pathogenesis are unknown

• Alpha-synuclein accumulates in oligodendrocytes (Glial Cytoplasmic Inclusions)
  • Associated with neuronal loss in striatum, substantia nigra, and cerebellum as well as widespread demyelination
Experimental Set-up

• Expression of alpha-synuclein by oligodendrocytes?
  • Oligodendrocytes do not normally express alpha-synuclein
  • Previous studies looking at alpha-synuclein mRNA in MSA oligodendrocytes were inconclusive

• Transmission/propagation of alpha-synuclein to oligodendrocytes from other cells?
a-synuclein is highly expressed in melanoma cell lines and tissue (E and F), but not in non-melanocyte cutaneous carcinoma (not shown) or normal skin (G and H)
Melanoma-Related Protein Staining

Positive controls of IHC antibodies using skin samples

α-MITF staining shows melanocyte nuclei

Secondary antibody only control
Melanoma-Related Proteins in MSA

Control Cerebellum

MSA Case Cerebellum
Examining the Pathogenesis of MSA

• Unlikely that MSA oligodendrocytes are expressing alpha-synuclein because of a phenotypic change

• Testing the Transmission Hypothesis
  • Brain lysates of MSA cases injected into tongues of wild-type and transgenic mice
    • Is it possible for pathological alpha-synuclein to spread from peripheral nerves to brain?
  • Experiment still ongoing
Conclusions

• Neurodegenerative diseases share a common theme of prion-like propagation of abnormal proteins
  • Alzheimer’s disease: Tau, amyloid beta
  • Parkinson’s disease: Alpha-synuclein
  • Multiple system atrophy: Alpha-synuclein?

• These processes of propagation offer new and exciting targets for potential treatments
  • Trials using monoclonal antibodies against pathological proteins ongoing
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