


Take home message

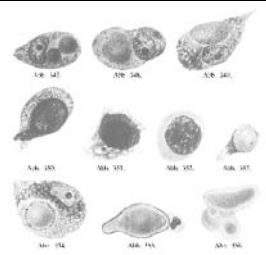

- Protein aggregation and defects in pathways that handle misfolded proteins are disrupted in Parkinson's disease.
- Identification of strategies to enhance protein quality control pathways may lead to novel therapeutics for Parkinson's disease and other neurodegenerative diseases.

Kalia and Lang, The Lancet, 2015



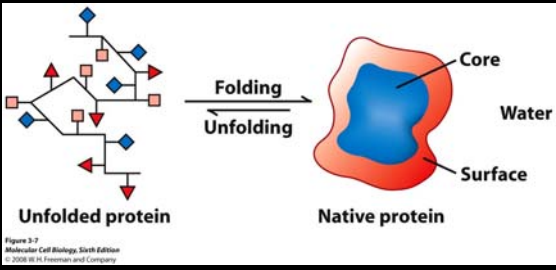
- Degenerative brain diseases share many elements (e.g. regional shrinkage, aggregated proteins)
- Similar mechanisms may be at play in AD, PD, FTD/ALS, and less common neurodegenerative diseases (e.g. HD)
- Many clues to disease mechanisms, but translation into therapy takes time

Frederic Heinrich Lewy

Lewy FH, Tonus und Bewegung, 1923

Why do proteins aggregate?



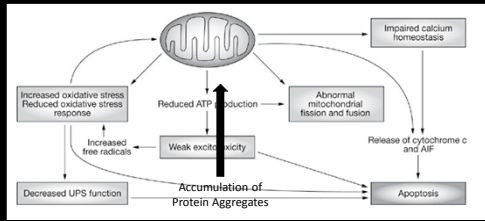
Unfolded protein → **Folding** → **Native protein**

Native protein → **Unfolding** → **Unfolded protein**

Labels: Core, Surface, Water

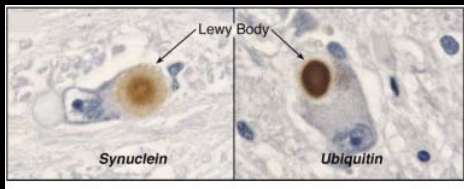
Figure 3-7 Molecular Cell Biology, Sixth Edition © 2008 W. H. Freeman and Company

Protein aggregates impair neuronal function

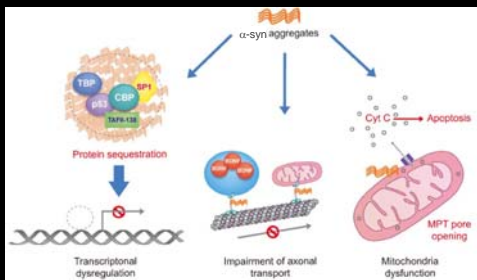


Henchcliffe C and Beal MF (2008) *Nat Clin Pract Neurol*

Some neurons with protein aggregates survive



How does protein aggregation affect neurons?

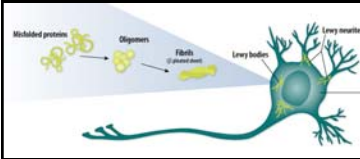


Adapted from Kim and Kim, *Exp Neurol*, 2014

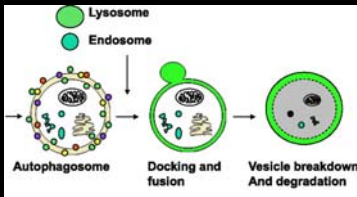
Protein aggregates can block traffic in the brain



But can we clean the streets?



Autophagy is a bulk degradation system



Molecular chaperones refold misfolded proteins

The diagram illustrates the energy landscape of protein folding. The y-axis represents energy, and the x-axis represents the progress of folding. It shows the path from an unfolded protein through folding intermediates to a native state. Chaperones are shown assisting in the folding process, preventing aggregation and amyloid fibril formation. A photo of a mailman is included as a visual metaphor for the chaperone's role in 'delivering' proteins to their native state.

Hartl et al., Nature, 2011

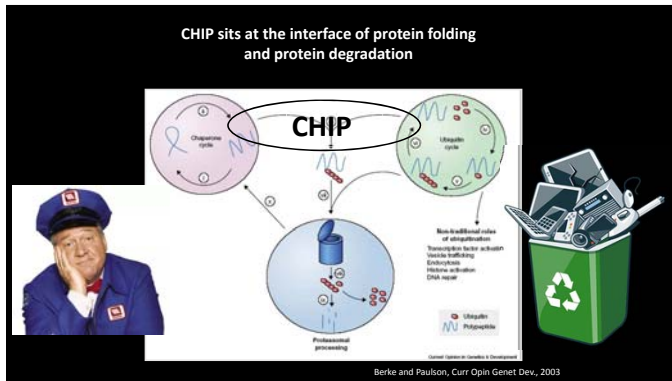
The ubiquitin proteasome system selectively degrades misfolded proteins

The ubiquitin system

The diagram shows the biochemical steps of the ubiquitin system. E1 (Ubiquitin-activating enzyme) is activated by ATP, forming a thioester bond with ubiquitin. E2 (Ubiquitin-conjugating enzyme) then receives ubiquitin from E1. E3 (Ubiquitin-ligase) facilitates the transfer of ubiquitin to a substrate protein, forming a polyubiquitin chain. The diagram also shows the inhibition of E1 and E2 by Thalidomide and Celebrex, and the inhibition of the proteasome by Bortezomib.

Passmore and Barford, Biochemical Journal, 2004

Thalidomide - targets the E3 ligase Celebrex
Bortezomib - targets the proteasome



Can we target these pathways to accelerate degradation of protein aggregates?

CHIP modulators

HSF1 activators
Neef et al., *Nat Rev Drug Discov*, 2011

Autophagy activators
Siddiqui et al., *JNeurosci*, 2015

USP14 Inhibitors
Lee et al., *Nature*, 2010

Happening in the Scaglione lab here at MCW.

Take home message

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Kalia and Lang, *The Lancet*, 2015
