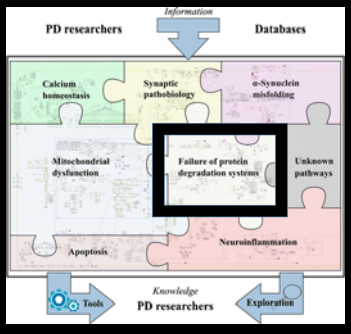
Parkinson's Disease | Making Sense of a Mysterious Disease

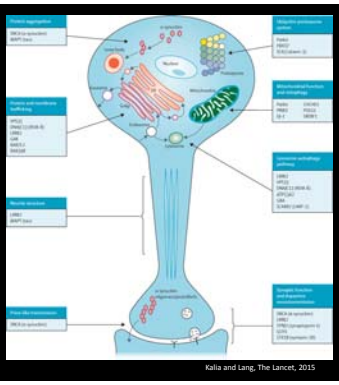
Conversations with Scientists: Neuroscience – Your Amazing Brain



Obeso JA, Rodriguez-oroz MC, Goetz CG, et al. Nat Med. 2010
Fujita KA, Ostaszewski M, Matsuoka Y, et al. Mol Neurobiol. 2014

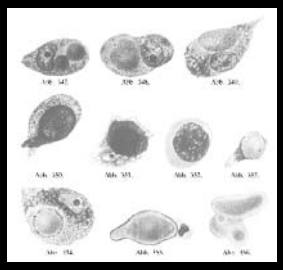
Take home message

- 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?

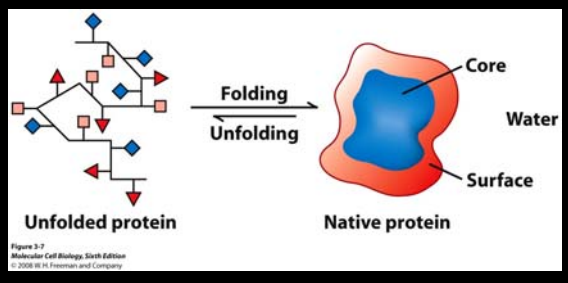
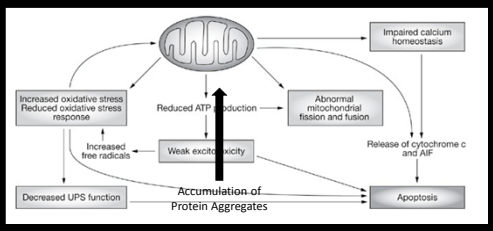


Figure 3-7
Molecular Cell Biology, Sixth Edition
© 2008 W. H. Freeman and Company

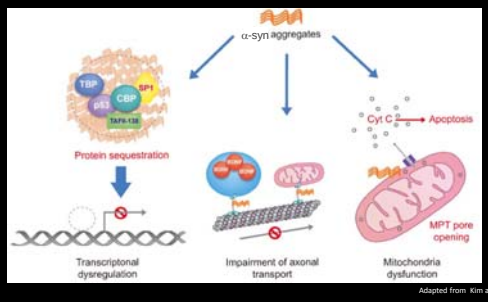
Protein aggregates impair neuronal function



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

Some neurons with protein aggregates survive

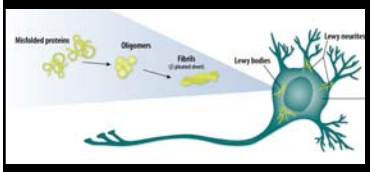
How does protein aggregation affect neurons?



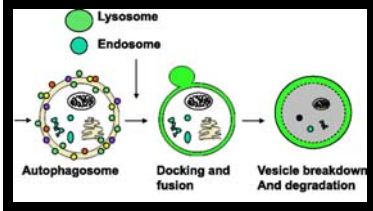
Adapted from Kim and Kim, Exp Neuro, 2014

Protein aggregates can block traffic in the brain

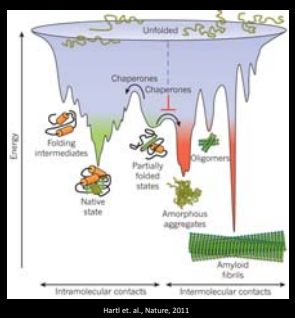
But can we clean the streets?



Autophagy is a bulk degradation system



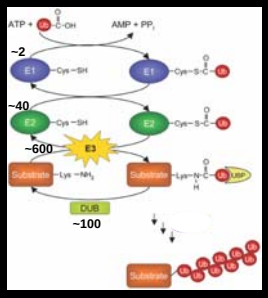
Molecular chaperones refold misfolded proteins



Hartl et. al., Nature, 2011

The ubiquitin proteasome system selectively degrades misfolded proteins

The ubiquitin system

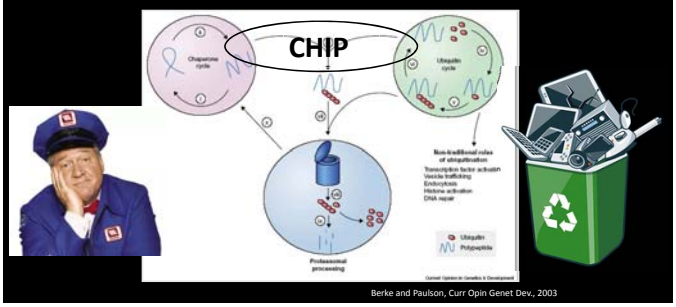


Passmore and Barford, Biochemical Journal, 2004

Thalidomide - targets the E3 ligase Celebron

Bortezomib - targets the proteasome

CHIP sits at the interface of protein folding and protein degradation



Berke and Paulson, Curr Opin Genet Dev., 2003

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

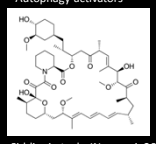
CHIP modulators

Happening in the Scaglione lab here at MCW.

HSF1 activators

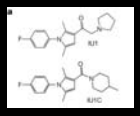
Neef et. al., Nat Rev Drug Discov, 2011

Autophagy activators



Siddiqui et. al., JNeurosci, 2015

USP14 Inhibitors



Lee et. al., Nature, 2010

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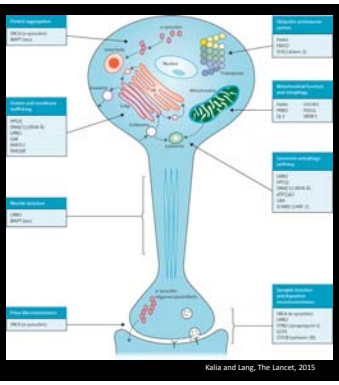

Kalia and Lang, The Lancet, 2015