

A Molecular Basis for the Protective Role of Protein Disulfide Isomerase in Parkinson's Disease

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Overview

- Meet protein disulfide isomerase (PDI)
- Cholera toxin and serendipity
- Neurodegeneration and PDI
- Project Goals

Protein Disulfide Isomerase

PDI is a chaperone

chaperones help other protein fold properly

chaperones prevent protein aggregation

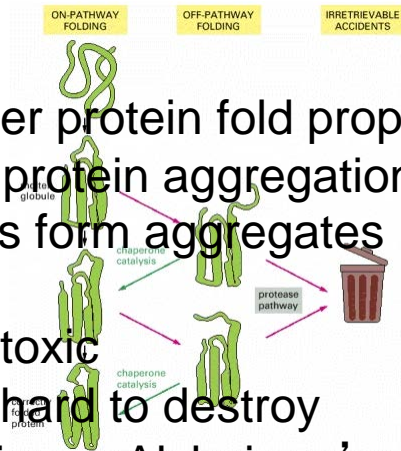
misfolded proteins form aggregates

Protein aggregates are toxic

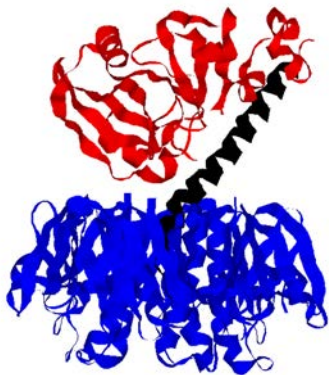
Protein aggregates are hard to destroy

$A\beta$ peptide aggregation = Alzheimer's

α -synuclein aggregation = Parkinson's



Cholera Toxin and PDI

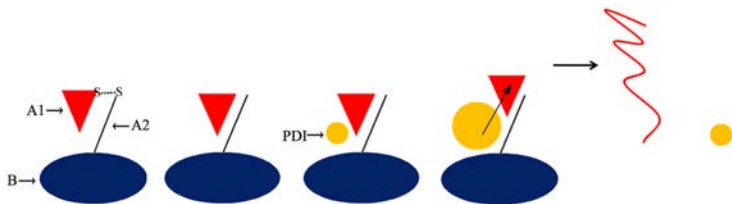


Cholera toxin

The active component of cholera toxin (CTA1; red) must be separated from the rest of the toxin in order to affect host cells.

PDI is responsible for separating the active component from the rest

Cholera Toxin and PDI

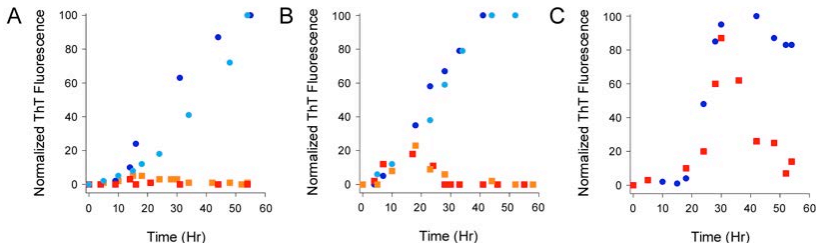


When PDI binds to CTA1, PDI unfolds
unfolded proteins are larger than folded
The expanded size of unfolded PDI pushes
PDI re-folds after its release from CTA1

PDI and Neurodegeneration

- PDI prevents protein aggregation
- Neurodegeneration results from protein aggregation
- PDI is linked to neurodegeneration
 - Non-functional PDI is found in Alzheimer's & Parkinson's diseases
 - PDI is found in $A\beta$ and α -synuclein aggregates
- Hypothesis:
 - The unfolding of PDI prevents & reverses protein aggregation
- Test:
 - PDI interaction with α -synuclein

PDI Prevents and Reverses Protein Aggregation



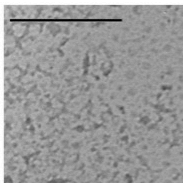
Circles: α -synuclein aggregation

Squares: α -synuclein aggregation + PDI

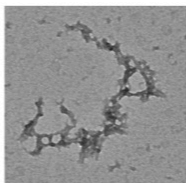
A. PDI added at 0 Hr

B. PDI added at 18 Hr

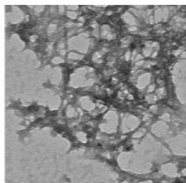
PDI Prevents and Reverses Protein Aggregation



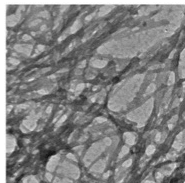
α -synuclein at 0 Hr



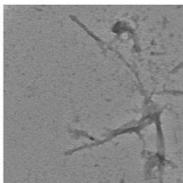
α -synuclein at 18 Hr



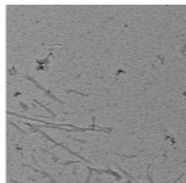
α -synuclein at 30 Hr



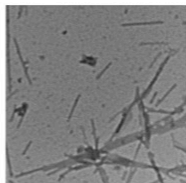
α -synuclein at 54 Hr



α -synuclein at 54 Hr
PDI addition at 0 Hr



α -synuclein at 54 Hr
PDI addition at 18 Hr



α -synuclein at 54 Hr
PDI addition at 30 Hr

Project Goals

- Demonstrate PDI unfolds upon contact with α -synuclein
- Demonstrate PDI unfolding is required to prevent and/or reverse α -synuclein aggregation
- Provide a molecular basis for the protective role of PDI in Parkinson's Disease
- PDI as a potential therapeutic intervention for neurodegenerative diseases

Thank You!

- Michael Taylor, Ph.D.
- Albert Serrano

- Drs. Suren Tautlian and Bo Chen (UCF)

- Questions?