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 proteins fold properly and prevent protein aggregation. Misfolded proteins form aggregates, which are toxic and hard to destroy. 

$\alpha$-synuclein aggregation = Parkinson’s disease 
$\beta$-peptide aggregation = Alzheimer’s disease
Cholera Toxin and PDI

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 of the toxin.
When PDI binds to CTA1, PDI unfolds. Unfolded proteins are larger than folded variants of the same protein. The expanded size of unfolded PDI pushes CTA1 away from the rest of the toxin. PDI then refolds after its release from CTA1. PDI unfolding is required to remove CTA1 from the rest of the toxin and is linked to the chaperone function of PDI.
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 Aβ 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: $\alpha$-synuclein aggregation
Squares: $\alpha$-synuclein aggregation + PDI
A. PDI added at 0 Hr
B. PDI added at 18 Hr
C. PDI added at 30 Hr

ThT is a dye that generates a fluorescent signal in the presence of aggregated protein.
PDI Prevents and Reverses Protein Aggregation
Project Goals

• Demonstrate PDI unfolds upon contact with $\alpha$-synuclein

• Demonstrate PDI unfolding is required to prevent and/or reverse $\alpha$-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!

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• Questions?