The Role of Peroxiredoxins in Alleviating Alzheimer’s Pathology

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Alzheimer’s Disease (AD)

• Unknown pathogenesis, while **oxidative stress** believed to be central to the progression of the disease

• Characterized by amyloid-β and tau protein aggregates in the brain (block normal neuronal signaling)

• Could redox-modifying proteins (**peroxiredoxins**) mitigate AD pathology?
Peroxiredoxins (Prx’s)

• Prx’s are proteins that confer resistance to oxidative stress via cellular redox and redox-mediated signaling

• Reduction in oxidative stress may alleviate AD symptoms
Special Interest: Prx 6

- Unique function: Phospholipase A2 activity

- Increase in inflammatory products could have a negative effect on AD pathology

- Net Benefits: PLA2 Antioxidant

![Diagram showing the role of PLA2 and COX in inflammation](image-url)
Why Peroxiredoxin 6?

The range of Peroxiredoxin 6 positive cell counts in different brain regions of gray and white matter in control and Alzheimer’s patients.
Support for Prx6 in AD

- Amyloid-beta infused Prx6 overexpression mice display accelerated Alzheimer’s

  Alzheimer’s disease -> increased Ab42
  
  Leads to
  
  Increased oxidative stress/ROS
  
  Activates Nrf-2 which relocates to nucleus
  
  Increased transcription of antioxidants = Peroxiredoxins
  
  Prx6 = increased PLA2 activity
  
  Increased inflammation
  
  Target
Conserved Pathway

- Inserted Human Aβ-42 transgene -> hallmark of AD pathology
- Perfect Model System
- Highly conserved pathway between Drosophila & humans
In the AD flies:

- Knockout the expression of Prx 1-6 via RNA hairpins

- Western Blots to confirm the knockouts of each Prx, as well as the presence of amyloid-beta plaques

- Measure and compare the different lines through several assays:
  - Lifespan
  - Oxidative Stress
  - Locomotor Activity
  - Morphology/cryo-sectioning
  - Western blots

RNA hairpin= Gene silenced
Two forms of Prx6 in the fruit fly: **Prx 2540** & **Prx 6005**

- **Prx2540** = has the PLA2 activity

- **Prx6005** = essentially the same protein **without** the PLA2

Upon single knockouts of each protein in an AD background, we will be able to determine if PLA2 is contributing to the progression of Alzheimer’s
Future Measurements

- Oxidative stress & Amyloid-beta plaque measurements at 10, 30, and 50 days of age for each line

- Lifespan curves will allow for direct comparison between lines

- Brain sectioning of each Prx-Alz line will allow for visual comparison
Works Cited

Fall Symposium
Summer Research Fellows

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