Amyloid Precursor Protein and Mitochondria

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Amyloid Pathology: 20-year prodrome

[Graph showing the progression of biomarkers (Aβ, Tau-related injury, Structural MR, Memory, Clinical function) from normal to MCI and Dementia stages.]

Hypotheses of Alzheimer’s Disease: Mitochondria

Inheritance Determines Baseline Mitochondrial Function and Density

Mitochondrial functional declines with age

A functional threshold is reached

- tau hyperphosphorylation and tangles
- amyloid beta plaque formation
- synaptic loss and degeneration
APP targeting to Mitochondria

Wilkins and Swerdlow
APP localizes to Mitochondria

*Human Brain (postmortem)*

**ND**

- Crude
- +Trypsin

**AD**

- Crude
- +Trypsin

<table>
<thead>
<tr>
<th></th>
<th>Crude</th>
<th>+Trypsin</th>
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</thead>
<tbody>
<tr>
<td>&lt;APP</td>
<td></td>
<td></td>
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<tr>
<td>&lt;CS</td>
<td></td>
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<tr>
<td>&lt;Calnexin</td>
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Mitochondrial APP Densitometry/Total Protein (AU)

- ND
- AD

**ND/AD diagnosis via ADNI**

Unpublished Data
Mitochondrial activity modulates APP localization

**Cell Culture**

*Increased Activity=Reduced mitochondrial APP*

*Decreased Activity=Increased mitochondrial APP*

Wilkins et al. 2021 JAD
Mitochondrial APP localization affects Aβ secretion

Cell Culture

$A\beta_42$ vs. Mitochondrial Localized $A\beta$PP

$r = -0.7391$ ***; least squares fit

$A\beta_40$ vs. Mitochondrial Localized $A\beta$PP

$r = -0.7427$ ***; least squares fit

$A\beta_42/A\beta_40$ vs. Mitochondrial Localized $A\beta$PP

$r = -0.9357$ ****; least squares fit
Mitochondrial APP localization affects Aβ secretion

Human Brain (postmortem)

\[ r=0.5418^*; \text{ least squares fit} \]

Mitochondrial APP Densitometry

<table>
<thead>
<tr>
<th>Stage</th>
<th>CERAD (Neuritic Plaques)</th>
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</thead>
<tbody>
<tr>
<td>Stage 0</td>
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<tr>
<td>Stage 1-2</td>
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<td>Stage 3</td>
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</table>

Unpublished Data
How do mitochondria affect APP and Aβ?
How does APP affect mitochondria?

Cell Culture

<table>
<thead>
<tr>
<th></th>
<th>High</th>
<th>Low</th>
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</thead>
<tbody>
<tr>
<td>WT</td>
<td>3M</td>
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</tbody>
</table>

Mitochondrial level of APP

<APP

<COX4I1

<HDAC

1.0  0.7

Unpublished Data
How does APP affect Mitochondria?

Cell Culture ETC function

WT=high mitochondrial APP
3M=low mitochondrial APP

Unpublished Data
How does APP affect Mitochondria?

Cell Culture-Mitophagy/Mitochondrial Turnover

WT = high mitochondrial APP
3M = low mitochondrial APP
How does APP affect Mitochondria?

Cell Culture-Mitochondrial mass/biogenesis

WT=high mitochondrial APP
3M=low mitochondrial APP

Unpublished Data
APP, Aβ, Mitochondria

Low activity = high APP

Low Aβ secretion
What does the field need?

1. To understand the function of APP and Aβ at mitochondria

2. Better models of AD and increased access to human tissue/samples

3. Increased collaboration

4. Train the next generation of scientists