The Role of RasA in Starvation-Induced Mitochondrial Elongation

An important protein for cancer therapeutics?

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The Year 1971:
The United States of America
The Man Behind the Metabolism: Otto Warburg

“There is today no other explanation for the origin of cancer cells, either specific or general, except a metabolic one. It is specified.”

-Otto Warburg, 1956
49 years later: Cancer Therapeutics

- Several therapeutic drugs decrease the cancer cell’s ability to use extra glucose
Mitochondria

Textbook

Reality

Elongated

Intermediate

Fragmented
Mitochondrial Dynamics

![Diagram of mitochondrial dynamics involving RalA and Drp1](image)
Glucose Deprivation leads to Mitochondrial Elongation

Glucose Starved

Untreated

Glucose

Elongated

Intermediate

Fragmented

Glucose Deprivation

Elongated

% morphology

0
20
40
60
80

- Fragmented
- Intermediate
- Elongated
Glucose Deprivation leads to Mitochondrial Elongation

- Untreated
- Glucose Starved
  (1hr)

- Glucose Deprivation

- Elongated

- Mitochondria
- Nucleus
Phosphorylation of Drp1 on Serine 637 is Necessary for Mitochondrial Elongation During Glucose Starvation
Question:
Is RalA involved in starvation induced mitochondrial elongation?
Methodology

1) Thaw cells

- Starve (hrs): 0, 2.5, 3.5
  - - RalA
  - + RalA

Identify Protein
Methodology

1) Thaw cells
2) Split cells
3) Starve cells
4) Harvest protein

<table>
<thead>
<tr>
<th>Starve (hrs)</th>
<th>0</th>
<th>2.5</th>
<th>3.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibody</td>
<td></td>
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[Diagram showing antibody binding to different stages of starved cells]
**RalA may be Involved in Starvation-Induced Mitochondrial Elongation**

**Loss of RalA prevents Induction of Drp1 S637 Phosphorylation**

<table>
<thead>
<tr>
<th>starve (hrs):</th>
<th>shScram</th>
<th>shRalA</th>
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</thead>
<tbody>
<tr>
<td>p-Drp1 (S637)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Drp1</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>RalA</td>
<td>1.0</td>
<td>1.5</td>
</tr>
<tr>
<td>GAPDH</td>
<td>1.5</td>
<td>1.5</td>
</tr>
</tbody>
</table>

**RalA GTP-Loading Changes Under Starvation**

**p-637-Drp1 Levels Change Under Starvation**
(In a similar pattern to RalA GTP-loading (?))
Implications

- Cancer therapy: Glucose inhibitors block cells’ use of glucose
- Mitochondria elongate to avoid degradation, and continue making energy for the cell
- If RalA is involved in this elongation, can inhibit RalA as well as using a glucose inhibitor
- Cell’s mitochondria won’t elongate, will be degraded
- Cancer cell may die
Thank you!

Kashatus Lab

Current Lab Members:
Left to Right: Ashley Ferguson, Sarbajeet Nagdas, Jennifer Kashatus, Aldo Nascimento, David Kashatus, Riley Trainor, Sarah Pollock

Past Lab Members:
Brian Chen, Lindsey Myers, Sarah Heuer, Allison Meadows

- College Science Scholars Program
- Beirne Carter Center for Immunology
- Mr. and Mrs. J. Randolph Hutcheson
- Friends and Family