Resveratrol Regulates Autophagy in Chronically Ischemic Myocardium

16th Annual C. Walton Lillehei Resident Research Forum

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No disclosures
Background

Autophagy

“Self Eating”
Background: Resveratrol
Serum lipid concentration

Chronic ischemia
Objective

Resveratrol $\approx$ Caloric restriction

? $+$ Autophagy
Methods: Study Design

ACC, n = 7
Ameroid Constrictor Control

HCC, n = 7
High Calorie/Cholesterol

HCRV, n = 6
High Calorie/Cholesterol + Resveratrol

4 Weeks
Ameroid placement to induce chronic ischemia

11 Weeks
Tissue Harvest
Ameroid Constrictor Placement
4 weeks
Coronary Catheterization
11 weeks
Results: Body Mass Index (BMI)

Week 4

Week 11

p = 0.82

p = 0.0042
Results: Blood Glucose

Week 11
30 minutes after 50 g dextrose IV

Blood Glucose (mg/dL)

ACC  |  HCC  |  HCRV

p = 0.0014
Schematic Model of Autophagy

- p70S6k
- Beclin 1
- ATG12
- ATG5
- LAMP 2
- LC3A II
- mTOR

Autophagy Induction → Phagophore → Autophagosome → Autolysosome
Results: Protein Expression

- Activated mTOR ↓ autophagy
- High cholesterol diet ↑ mTOR
- Resveratrol reverses this effect
Results: Protein Expression

- **p70S6K** $\uparrow$ autophagy induction
- High cholesterol diet $\downarrow$ p70S6K
- Resveratrol may blunt this effect
Results: Protein Expression

- High cholesterol diet $\downarrow$ LAMP 2
- Resveratrol blunts this effect
Results: Protein Expression

- LC3A II helps form autophagosome
- LC3A II ↑ with high cholesterol
- Resveratrol blunts this change

Ischemic Myocardium

Follow the processes of autophagy:

1. Phagophore
2. Autophagosome
3. Autolysosome

Graph showing fold change in LC3A-II expression:

- ACC
- HCC
- HCRV

Graph shows a significant increase in LC3A-II expression in HCC compared to ACC and HCRV. Resveratrol blunts this change. (p=0.017)
## Results: Protein Expression

### Non-Ischemic Myocardium

<table>
<thead>
<tr>
<th>Targets</th>
<th>ACC</th>
<th>HCC</th>
<th>HCRV</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>mTOR</td>
<td>1 ± 0.154</td>
<td>1.64 ± 0.272</td>
<td>0.94 ± 0.383</td>
<td>0.16</td>
</tr>
<tr>
<td>p-mTOR</td>
<td>1 ± 0.172</td>
<td>1.82 ± 0.478</td>
<td>0.92 ± 0.100</td>
<td>0.22</td>
</tr>
<tr>
<td>P70S6K</td>
<td>1 ± 0.199</td>
<td>1.05 ± 0.112</td>
<td>1.03 ± 0.170</td>
<td>0.98</td>
</tr>
<tr>
<td>Beclin 1</td>
<td>1 ± 0.163</td>
<td>0.56 ± 0.039</td>
<td>0.75 ± 0.068</td>
<td>0.0098*</td>
</tr>
<tr>
<td>ATG 5/12</td>
<td>1 ± 0.332</td>
<td>0.73 ± 0.133</td>
<td>0.87 ± 0.291</td>
<td>0.72</td>
</tr>
<tr>
<td>LAMP1</td>
<td>1 ± 0.123</td>
<td>0.92 ± 0.094</td>
<td>0.97 ± 0.176</td>
<td>0.89</td>
</tr>
<tr>
<td>LAMP2</td>
<td>1 ± 0.201</td>
<td>0.61 ± 0.062</td>
<td>0.69 ± 0.197</td>
<td>0.18</td>
</tr>
<tr>
<td>LC3A-II</td>
<td>1 ± 0.149</td>
<td>0.70 ± 0.106</td>
<td>0.88 ± 0.165</td>
<td>0.28</td>
</tr>
<tr>
<td>LC3B-II</td>
<td>1 ± 0.135</td>
<td>0.66 ± 0.051</td>
<td>0.86 ± 0.123</td>
<td>0.063</td>
</tr>
</tbody>
</table>
High Cholesterol

mTOR

p70S6k

Beclin 1

Autophagy Induction

ATG12

ATG 5

LAMP 2

LC3A II

Phagophore

Autophagosome

Autolysosome
High Cholesterol

mTOR

p70S6k

RV

ATG12

ATG 5

Beclin 1

LAMP 2

LC3A II

Autophagy

Induction

Phagophore

Autophagosome

Autolysosome
Limitations

• Limited number of subjects
• Treatment length and dose
• Single time point
Conclusions

• High calorie diet results in disturbances in autophagy signaling

• Resveratrol blunts many of the effects

• Benefits of resveratrol may be related to its regulation on autophagy signaling
Thank you

Dr. Frank W. Sellke
Dr. Nassrene Y. Elmadhun
Dr. Michael P. Robich
Rahul S. Dalal MS-2
Resveratrol Regulates Autophagy in Chronically Ischemic Myocardium

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Harvard Medical School, Boston, MA
100 mg/Kg/day ≈ 140 Liters of wine per day
Results: Protein Expression

- High cholesterol ↑ Beclin 1
- No change with resveratrol

Beclin 1

Autophagy Induction → Phagophore → Autophagosome → Autolysosome

Ischemic Myocardium

![Graph showing Beclin1 expression levels.](image-url)
Results: Protein Expression

- High cholesterol ↓ ATG 12-5
- Resveratrol does not alter this step