Heart Failure Progression: Targeting Hypertrophy

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No disclosures
Acute Myocardial Infarction: Dramatic Clinical Advances

% Mortality (in hospital)

<table>
<thead>
<tr>
<th>Year</th>
<th>% Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>pre-CCU</td>
<td>30</td>
</tr>
<tr>
<td>CCU era</td>
<td>15</td>
</tr>
</tbody>
</table>

- defibrillation
- hemodynamic monitoring
- beta-blockade
- ASA
- thrombolytic Rx
- PCI
- reperfusion
Transformed to a Chronic Disease: Heart Failure

![Image of a heart failure x-ray and a heart model]

CHF Prevalence in US (millions)

- 1990: 3.0
- 2010 est: 4.2
- 2030 est: 5.7
Epidemic of Heart Failure

AHA Heart Disease and Stroke Statistics, 2007
Chronic Heart Failure

Failed Therapies

Beta-adrenergic agonists
Phosphodiesterase inhibitors
Ca$^{2+}$ channel activators
Sarcomere Ca$^{2+}$ sensitizers
Cytokine antagonists
...

Successful Therapies

<table>
<thead>
<tr>
<th>1970</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>Diuretics</td>
</tr>
<tr>
<td>Digitalis glycosides</td>
<td>Digitalis glycosides</td>
</tr>
<tr>
<td>RAAS antagonists</td>
<td>Beta-blockade</td>
</tr>
<tr>
<td>Devices!</td>
<td></td>
</tr>
<tr>
<td>Implantable defibrillators</td>
<td>Resynchronization therapy</td>
</tr>
</tbody>
</table>
Cardiac Responses to Stress

↑ heart rate

↑ stroke volume

hypertrophy
Hypertrophic Growth of the Heart

...encompasses many molecular and cellular responses:

↑ protein synthesis
re-activation of "fetal" genes
sarcomere recruitment and assembly
action potential prolongation
fibrosis
Cardiac Hypertrophy

Adaptive
- Normalized wall stress
- ↓ Myocardial O₂ demand

Maladaptive
- ↑ Risk of heart failure
- ↑ Risk of arrhythmia
Slowing Disease Progression

Transcriptional Control of Pro-hypertrophic Genes

Activation of Anti-Growth Mechanisms
Stress Signals

\[ \text{calcineurin} \rightarrow \text{kinases} \]

\[ \text{Ca}^{2+} \rightarrow \text{NFAT} \leftrightarrow \text{MEF2} \]

Cardiac Growth & Remodeling Genes

Eric Olson et al
TSA blunts pressure-overload hypertrophy
TSA blunts cardiomyocyte growth and fibrotic change

Kong et al., *Circulation* 2006
Scriptaid blunts hypertrophy

Kong et al., *Circulation* 2006
TSA-blunted hypertrophy: Similar survival and preserved LV size and performance

Kong et al., *Circulation* 2006
Preservation of systolic function

Kong et al., Circulation 2006
TSA blunts hypertrophy-associated MHC isoform switch

Kong et al., *Circulation* 2006
Slowing Disease Progression

Transcriptional Control of Pro-hypertrophic Genes

Activation of Anti-Growth Mechanisms
Downstream Targets

- FoxO
- E3 ubiquitin ligase
- Fas ligand
- P27Kip
- Apoptosis
- Protein degradation
- Cell cycle arrest
FoxO antagonizes calcineurin

Ni et al., Circulation 2006.
FoxO blocks hypertrophy

**Untreated vs. Ang II**

- GFP
- FoxO1-GFP

**Relative $^3$H-leucine Incorporation/DNA**

- GFP
- FoxO1-GFP
- caFoxO1-GFP

**Cell Surface Area ($\mu m^2$)**

- GFP
- FoxO1-GFP

**Cell Cross Sectional Area, $\mu m^2$**

- GFP
- FoxO1-GFP

**$\beta$-MHC mRNA levels relative to GAPDH**

- GFP
- caFoxO1-GFP
FoxO blocks agonist-induced activation of calcineurin

Ni et al., *Circulation* 2006.
FoxO3-null mice are hypertrophic

Ni et al., *Circulation* 2006.
FoxO triggers Akt, an upstream repressor

Ni et al., PNAS 2007, In Press.
Foxo activation induces insulin resistance

A novel mechanism of insulin resistance in heart

Ni et al., PNAS 2007, In Press.
Conclusion

• Hypertrophic growth of the myocardium is a novel target for therapeutic intervention in heart failure.

• Strategies to block pro-growth pathways and/or activate anti-growth mechanisms warrant further evaluation.
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- Yanggan Wang
- Zhengyi Wang

## Collaborators

- Beverly Rothermel, PhD
- Eric Olson, PhD
- Rhonda Bassel-Duby, PhD
- Beth Levine, MD
- James Richardson, DVM, PhD
HDAC inhibition is a promising strategy to target pathological remodeling of the stressed ventricle.
Foxo transcription factors inhibit cardiomyocyte hypertrophy due, at least in part, to their suppression of calcineurin signaling.
Disease-Associated Cardiomyocyte Stress

Biomechanical stress
- Pressure Stretch

Neurohumoral stress
- RAAS
- Adrenergic hormones
- Cytokines
- Vasoactive peptides
- Growth factors

Altered gene expression
- Transcript processing
- Post-translational mechanisms
“Never, ever, think outside the box.”
Heart Failure Progression

cell growth

cell death?
Heart Failure Epidemic: Incidence per 1000 person-years

Potential New Strategies to Treat Heart Failure

• Blocking pro-growth (hypertrophic) pathways
  HDAC inhibitors

• Activating anti-growth (atrophic) pathways
  Foxo

• Targeting programmed cell death
  Autophagy
“Whoa—way too much information.”