Pathological Cardiac Hypertrophy and Failure: Redox Mechanisms

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Learning objectives

- Distinguish between physiological and pathological hypertrophy of the heart
- Identify major sources of ROS in the heart that underlie hypertrophy and failure
- Identify redox-sensitive targets of ROS that mediate pathological hypertrophic signaling
- Define the anti-hypertrophic roles of thioredoxin (Trx) and glutaredoxin (Grx)
What is cardiac hypertrophy?

- Adaptive/maladaptive enlargement of the heart in response to increased hemodynamic stress.
Physiological vs pathological hypertrophy

Physiological stimuli:
- Chronic exercise
- Pregnancy

Physiological hypertrophy:
- Increase in myocyte length > increase in myocyte width

Pathological stimuli:
- Hypertension
- Myocardial infarction
- Genetic polymorphisms
- Altered cardiac metabolism (e.g., diabetes)

Pathological hypertrophy:
- Increase in myocyte length < increase in myocyte width

Hypertrophic cardiomyopathy

Myocardial infarction (MI)

Multiple factors underlying hypertrophy

- Physiological Hypertrophy
  - Fatty Acid oxidation
  - Mitochondrial biogenesis
  - Protein synthesis
  - Extracellular matrix

- Pathological Hypertrophy
  - Inflammation
  - Apoptosis
  - Glycolysis
  - Fetal isoforms

Dorn GW, Hypertension 49:962-970, 2007
Oxidative stress and heart hypertrophy/failure

Rozanski GJ, In: Redox Biochemistry, Wiley Interscience, pp 204-211, 2008
ROS and GSH in myocytes from hypertrophied hearts

Sham cell

Hypertrophied cell; Post-MI

A

TEMPO-9-AC

B

mBCl

Fluorescence (counts/m$^3$)

0
10
20
30

Fluorescence (counts/m$^3$)

0
10
20
30

[GSH] (amol/m$^3$)

0
1
2
3
4
5
Sham
Post-MI

*
Physiological vs pathological hypertrophy: signaling

![Diagram showing signaling pathways for physiological and pathological hypertrophy]

**Physiological Hypertrophy**
- GF
- GFR
- PI3K
- PIP3
- Akt
- p-Akt

**Pathological Hypertrophy**
- NH
- GPCR
- Gαq
- PLCβ
- PIP2
- DAG + IP3
- PKC
- Ca++

**Key Pathways**
- PIP2, phosphatidylinositol bisphosphate
- DAG, diacylglycerol
- PKC, protein kinase C

*Modified from Dorn GW, Hypertension 49:962-970, 2007*
Pathological signaling; redox-sensitive steps

NADPH oxidase (NOX) generation of ROS

- **Nox1**, vascular smooth muscle
- **Nox2**, cardiomyocytes, endothelial cells, fibroblasts and inflammatory cells
- **Nox3**, not reported in the cardiovascular system
- **Nox4**, all cardiovascular cell types
- **Nox5**, human endothelial cells/vascular smooth muscle

Chronic Ang II vs aortic banding (pressure overload)

A

Heart/body weight (mg/g)

WT

**

Vehicle

Ang II

B

LV/body weight ratio (mg/g)

WT

**

Sham

Band

NOX2^{-/-}

gp91^{phox/-}


NOX4 up-regulated by aortic banding

ROS activation of Ras

Ang II, α-agonists, ET-1

GPCR

Nox2 oxidase

ROS

ERK-1/2

Ras

NFAT

Other transcription factors

JNK/p38/NF-κB

Gene expression
Cys 118 in Ras

Thiol oxidation of Ras by α-adrenergic agonist

Kuster GM, et al., Circulation 111:1192-1198, 2005
Inhibition of cell hypertrophy by Trx1

Kuster GM, et al., Circulation 111:1192-1198, 2005
Ras activation by mechanical stretch (strain)

Pimentel DR, et al., J Mol Cell Cardiol 41:613-622, 2006
Inhibition of Ras activation by Grx1 over-expression

Pimentel DR, et al., J Mol Cell Cardiol 41:613-622, 2006
Strain, Ras and hypertrophy

Strain → ROS → Catalase

Ras → Ras

SH

SSG

Grx1

MEK → ERK

Hypertrophy
ROS activation of ASK1
Thioredoxin system in hypertrophied LV

NADPH → TrxR1 → Trx1 → Protein

ASK1-Trx1 binding

**A**

LV

<table>
<thead>
<tr>
<th></th>
<th>Sham</th>
<th>Post-MI</th>
<th>Sham</th>
<th>Post-MI</th>
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<tbody>
<tr>
<td>LV</td>
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<td>SE</td>
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IP: ASK1

WB: Trx1

**B**

Sham (4)

Post-MI (4)

Post-MI + IGF-1 (4)

Post-MI + AF + IGF-1 (4)

IGF-1, Insulin-like growth factor-1

AF, Auranofin (TrxR inhibitor)

Effect of IGF-1 on JNK and p38 activity

A

B

Redox regulation of ASK1-JNK-p38 signaling
NF-κB and hypertrophy

Redox-sensitive step(s) in NF-κB activation

NIK, NF-κB inducing kinase
MEKK-1, MAP kinase kinase-1
IKK, IκB kinase
IκB, Inhibitory protein
Role of TRP14 in hypertrophy?

TRP14, Thioredoxin-related protein 14
LC8, Dynein light chain 8
DPI, Diphenyleneiodonium
BHA, Butylated hydroxyanisol

Redox control of gene repressors/activators


Gene expression

Ang II, α-agonists, ET-1

GPCR

Nox2 oxidase

ROS

ERK-1/2, Ras, ASK-1

NFAT, JNK/p38/NF-κB

Histone Deacetylation

Gene Repression

Histone Acetylation

Gene Activation

HAT, histone acetyltransferase
HDAC, histone deacetylase
TF, transcription factor

Redox active Cys667/669 in HDAC4

Ago T, et al., Cell 133:978-993, 2008

NLS, Nuclear localization signal
NES, Nuclear export sequence
PE, Phenylephrine (α-adrenergic agonist)
Nuclear export of HDAC4 stimulated by CaMKII

Redox-sensitive Met 281/282 in CaMKII

Erickson JR, et al., Cell 133:462-74, 2008
Oxidation/phosphorylation of HDAC4
Summary

Ang II, α-agonists, ET-1

GPCR

Nox2 oxidase

ROS

ERK-1/2

Ras

ASK-1

JNK/p38/NF-κB

Gene expression

Cys 118
Trx1 (Ang II)
Grx1 (stretch)

HDAC4 (Cys 667/669)
Trx1/TBP-2
HDAC4 (Thr 287)
CaMKII (Met 281/282)
MsrA (Trx1)

Kinases/Phosphatases (IKK)
TRP14 (LC8)
References
