Presenter Disclosure Information

- Osamu Yamaguchi
- *Mitochondrial Permeability Transition and Non-apoptotic Cell Death*

FINANCIAL DISCLOSURE: None

UNLABELED/UNAPPROVED USES DISCLOSURE: None
Mitochondrial Permeability Transition and Non-apoptotic Cell Death

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Osaka University Graduate School of Medicine
Increased Afterload / Loss of Contactile Elements

Increased Mechanical Load (Wall Stress)

Activation of Neurohumoral Factors and Cytokines

Activation of Intracellular Signaling Pathways

Apoptosis

Necrosis

Heart Failure
Modes of Cell Death

**Apoptosis**
- Cytochrome c release
- Apoptotic death
- Active cell death

**Necrosis**
- $\Delta\psi$ loss
- Necrotic death
- Passive cell death

**Autophagy**
- Bulk degradation
- Autophagic death
- Autophagic cell death
The role of apoptosis in cardiac remodeling

Mechanial stress → ROS → ASK1 → JNK

Heart failure

Pressure overload

Myocardial infarction

Control

KO

Raf-1

KOxASKKO

Control

KO

Raf-1

ERK1/2

p38

NF-κB

Survival

Apoptosis

Control

KO

Pressure overload

p38α

Control

KO

ASK1 is Activated by Neurohumoral Factors and Cytokines in Cardiomyocytes in Vitro

Angiotensin II
Endothelin-1
TNF-α

Ca²⁺

ROS

Pyk2, Rac, NADPH oxidase

ASK1

Apoptosis

Heart Failure

CaMKII

Yamaguchi, et al. PNAS 2003
Hirotani, et al. J Mol Cell Cardiol 2004
Kashiwase, et al. BBRC. 2005
ASK1 is Activated in Response to Pressure Overload or Following MI


mice

ASK1 kinase assay

Pressure Overload

[caption]

Myocardial Infarction

[chart]

human

ASK1 kinase assay

Control

Heart failure
Reactive Oxygen Species, \( \text{Ca}^{2+} \)

PTP: Permeability Transition Pore

Mitochondria

\( \Delta \psi \) loss (ATP decrease)

Necrotic Death
Effect of CypD Ablation on Ischemia-Reperfusion Injury

(Nature 2005, Nakagawa and Yamaguchi et al.)

Ischemia
30min
Reperfusion
120min

Wild Type

CypD−/

Area at Risk (%)
Infarct Size (%)

Wild Type
CypD−/

n.s.
p<0.01

Wild Type
CypD−/
Effect of ASK1 Ablation on Ischemia-Reperfusion Injury

(BBRC 2005, Watanabe and Yamaguchi et al.)

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**Area at Risk (%)**

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**Infarct Size (%)**

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- n.s.
- p<0.01
- *
Pressure Overload | Reactive Oxygen Species

Mitochondria

- OMM
- IMS
- IMM
- Matrix
- Ca$^{2+}$
- H$^+$
- Δψ

PTP

- CypD

AS 1

- Apoptotic Death

MPT

- Necrotic Death

Heart Failure
Cardiac-specific Atg5−/− Mice

(Nature Medicine 2007)

10 months old

(Autophagy 2010)

ER stress
apoptosis
abnormal mitochondria
Ca^{2+}
apoptosis
necrosis
Mitochondria
autophagy