Introduction to ROS in the Cardiovascular System

John F. Keaney, Jr., M.D.
UMass Medical School
Worcester, MA
Role of ROS in CV Disease: Antiquated

Circulating monocytes

Native LDL

Resident monocyte-macrophage

Vessel lumen

Endothelial cells

Endothelial injury

Endothelial dysfunction

Subendothelial space

Smooth muscle

Cell-mediated oxidation

Oxidized LDL

Foam cell

Foam-cell necrosis

A

B

C

D

E

NEJM, 1997
**Antioxidant Defenses**

Enzymatic Systems: CAT, SOD, GPX
Non-enzymatic systems: Glutathione, Vitamins

**Endogenous Sources**

Mitochondria
Peroxisomes
Lipoxygenases
NADPH Oxidases
Cytochrome P450

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**ROS/RNS**

**Impaired Physiologic Function**

- Decreased Repair
- Decreased Adaptive Responses
- Vascular and Myocardial Disease

**Homeostasis**

Normal

**Impaired Physiologic Function**

- Random Oxidation
- Specific Signal Pathways
- Vascular and Myocardial Disease

Adapted from Finkel and Holbrook, 2007
NADPH Oxidases

Neutrophil “Burst” Oxidase

NADPH Oxidase (Nox) Enzyme Family

Bedard and Krause, *Physiol. Rev.* 2007;87
Contemporary ROS and CV System: Major Areas of Influence

Cardiac Function
Hypertrophy

Atherosclerosis
Hypertension

Angiogenesis
Vascular Repair
Contemporary ROS and CV System: Major Areas of Influence

- Cardiac Function
- Hypertrophy
- Atherosclerosis
- Hypertension
- Angiogenesis
- Vascular Repair
NADPH Oxidase (Nox) Enzyme Family

Bedard and Krause, Physiol. Rev. 2007;87
Nox2 Influences Cardiac Remodeling After Myocardial Infarction

- Less pathologic heart remodeling
- Reduced change to the fetal gene program
- Less apoptosis

Hypertension. 2008 Feb;51(2):319-25
NADPH Oxidase (Nox) Enzyme Family

Bedard and Krause, *Physiol. Rev.* 2007;87
Trans Aortic Constriction Model
Cardiac Nox4 is deleterious in pressure overload

Kuroda J et al. PNAS 2010;107:15565-15570

- Less pathologic hypertrophy
- Improved function (ejection fraction)
- Less apoptosis

Kuroda J et al. PNAS 2010;107:15565-15570
Nox4 Impacts Multiple ROS Sources

Kuroda J et al. PNAS 2010;107:15565-15570
Interaction of ROS Sources

Cave et. al. Antioxid. Redox Signal. 8, 691–728
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NADPH Oxidase Activity and Atherosclerosis

- ApoE(-/-) mice with or without p47phox
- Animals on chow followed for 30 weeks
- ROS production measured by DHE staining
- Atherosclerosis determined by aortic lipid content

What about hypertension?
Renin-Angiotensin System

- **Kidney** → **Renin** → Angiotensinogen → AI → **ACE** → AII
  - **AI** → Adrenal Cortex → Aldosterone
  - **AII** → Pituitary → ADH → Renal Sodium & Fluid Retention
  - **AII** → Thirst

- **AII** → Systemic Vasoconstriction
- **AII** → Cardiac & Vascular Hypertrophy
- **AII** → Increased Blood Volume
NADPH Oxidase (Nox) Enzyme Family

Bedard and Krause, Physiol. Rev. 2007;87
Nox2 and Hypertension

- Less ROS produced from blood vessels
- Less rise in blood pressure
- Less vascular hypertrophy

Not all ROS sources are equal!
NADPH Oxidase (Nox) Enzyme Family

Bedard and Krause, *Physiol. Rev.* 2007;87
BP and Hypertrophy are Distinct

Matsuno, K. et al. Circulation 2005;112:2677-2685
Contemporary ROS and CV System: Major Areas of Influence

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- Atherosclerosis
- Hypertension
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Bedard and Krause, *Physiol. Rev.* 2007;87
Bone Marrow Nox2 is Important for Ischemia-Induced Angiogenesis

- Lack of Nox2 impairs ischemia-induced angiogenesis
- This effect is most prominent in bone marrow

Nox2 Modifies Arterial Injury

Chen et al., *PNAS* 2004;101:13014-13019
How about other ROS Sources?
Mitochondrial ROS are Important for Hypoxic Responses

Guzy et al., Cell Metabolism, 2005
Take Home Points

• ROS are ubiquitous, and serve as cellular messengers
• ROS responses are generally linked to injury and repair responses
• ROS sources and the regulation of these sources has, thus far, proven the most fruitful means of impacting disease
• NADPH oxidases are one important source of ROS in the cardiovascular system
What we do not yet know

• Which source(s) of ROS are specific for certain pathologic disorders
• How do the different source(s) of ROS relate to each other
• What are the “normal” mechanisms for specificity of ROS species
• Which ROS/RNS are most important in specific disease(s)