Introduction to ROS in the Cardiovascular System

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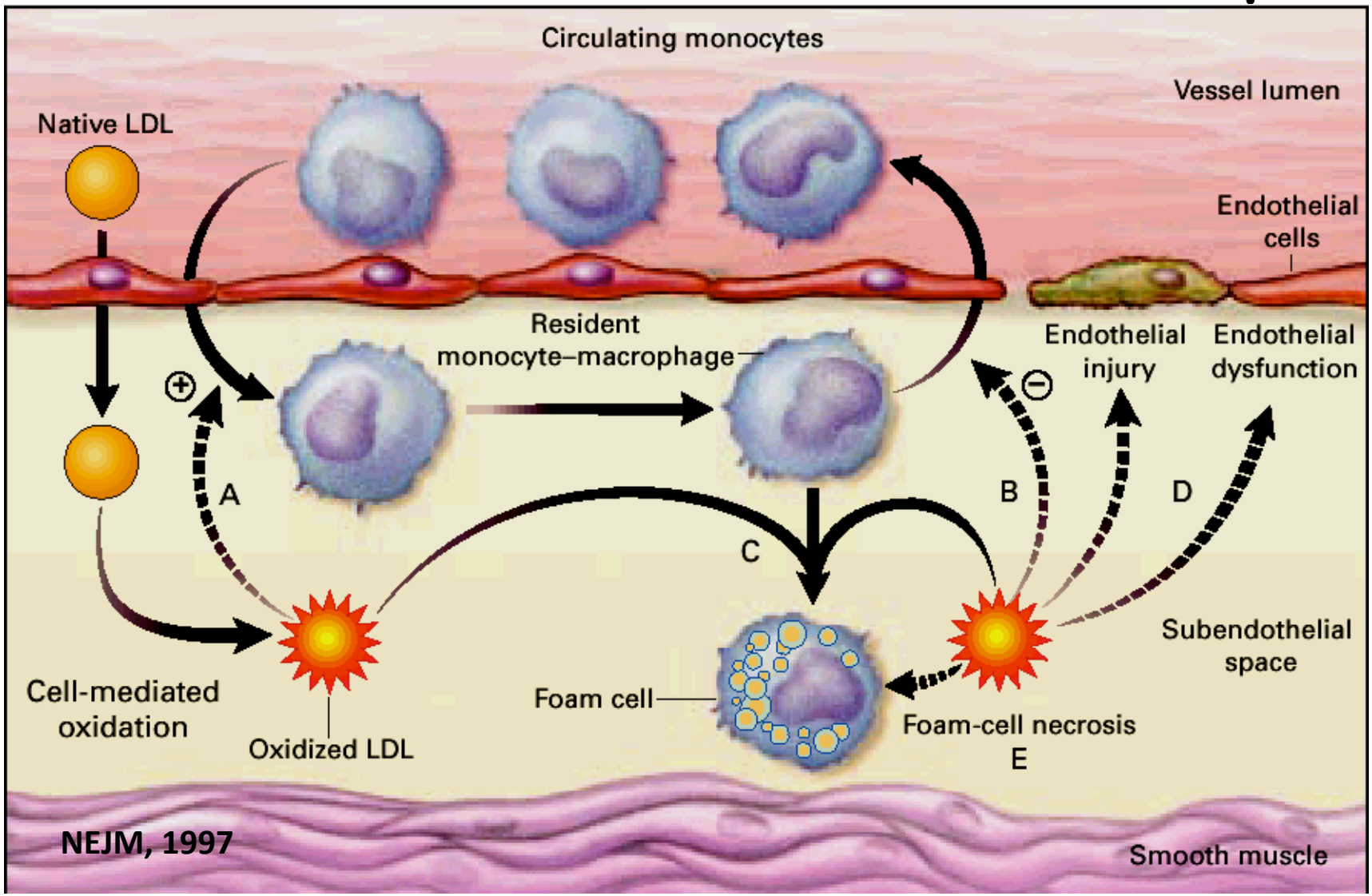
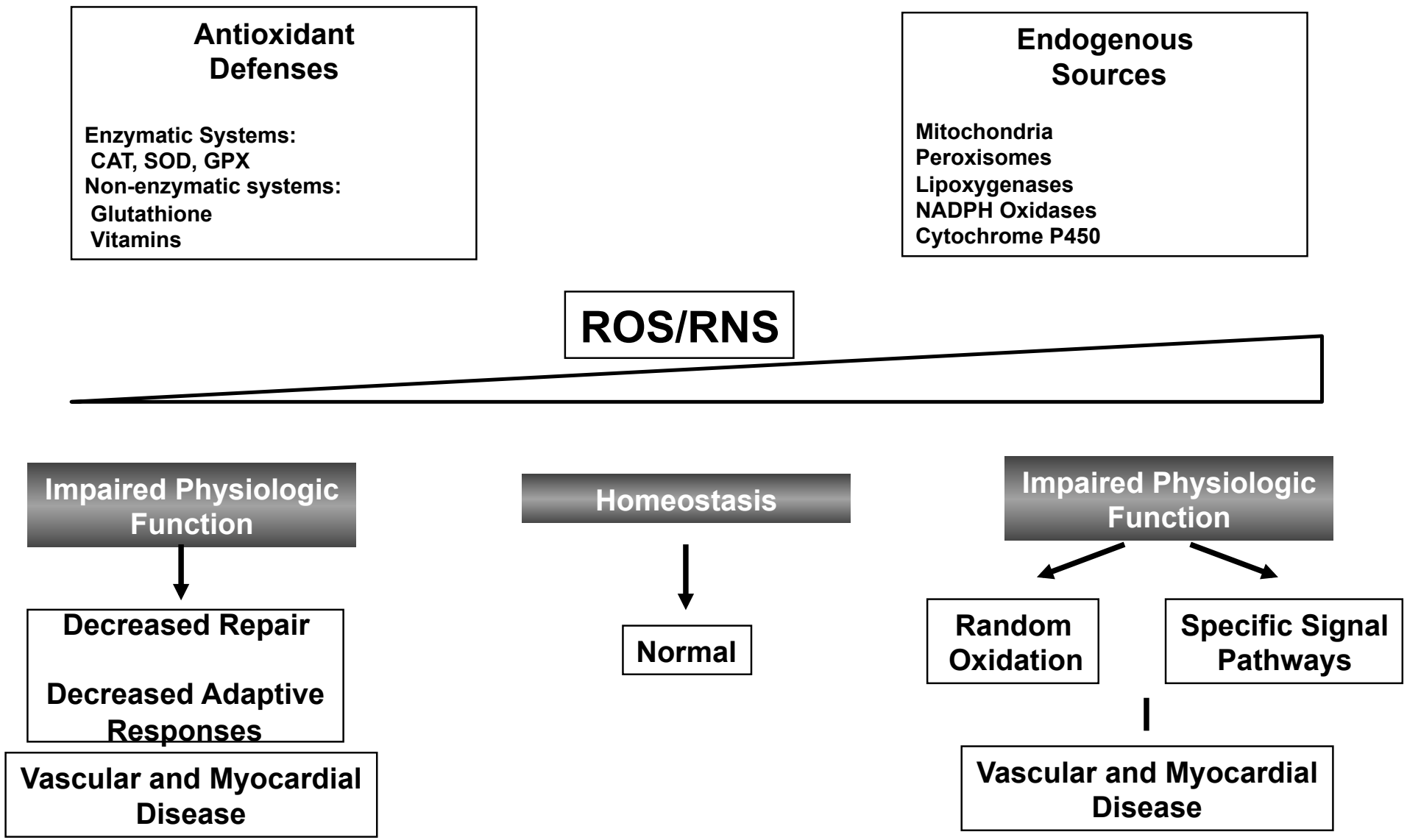
Worcester, MA

Role of ROS in CV Disease: Antiquated

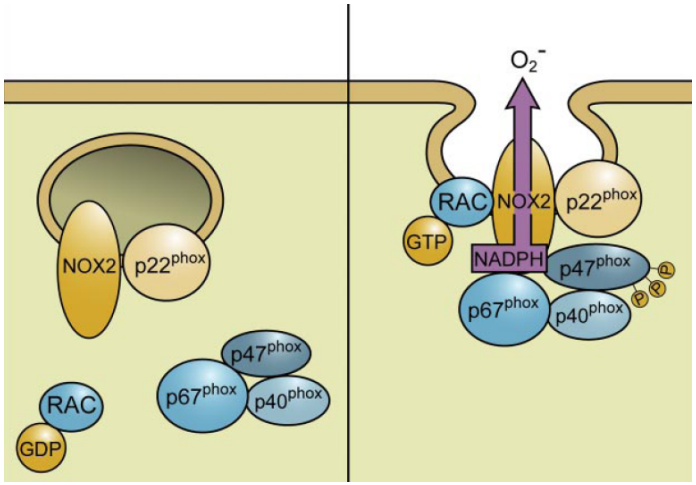




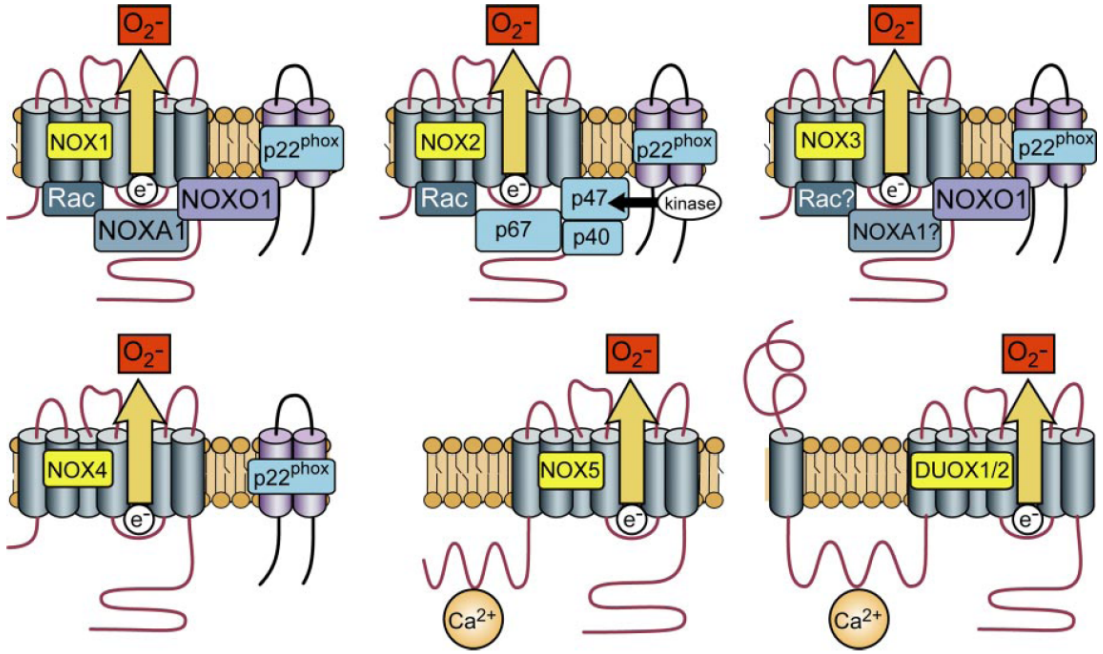
Adapted from Finkel and Holbrook, 2007

NADPH Oxidases

Neutrophil "Burst" Oxidase

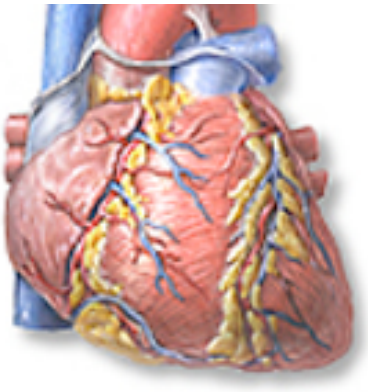


NADPH Oxidase (Nox) Enzyme Family

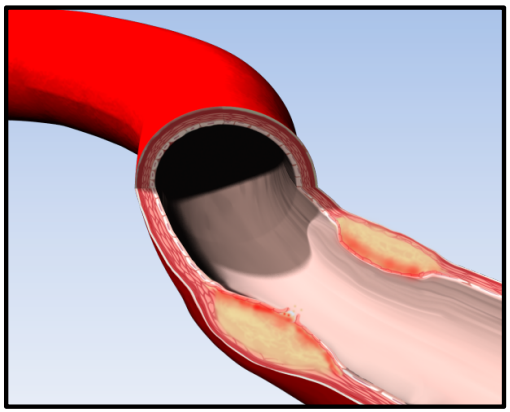


Bedard and Krause, *Physiol. Rev.* 2007;87

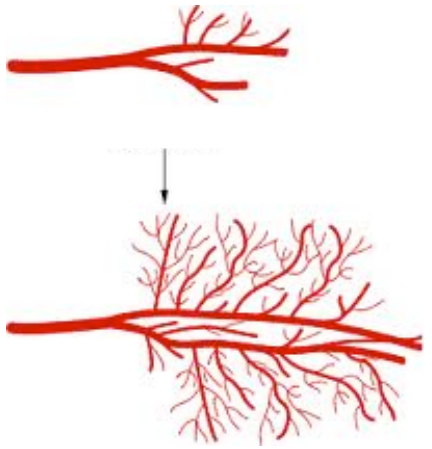
Contemporary ROS and CV System: Major Areas of Influence



Cardiac Function
Hypertrophy

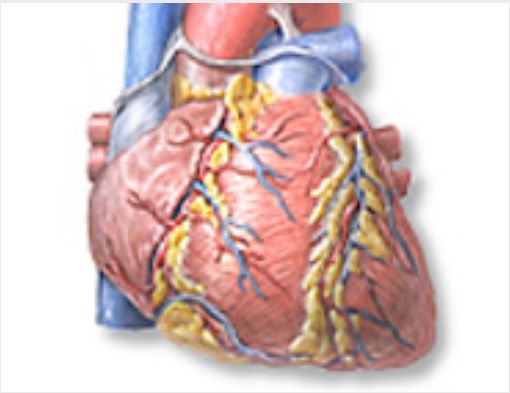


Atherosclerosis
Hypertension

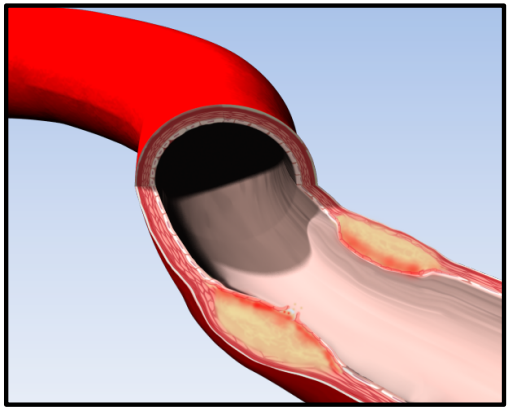


Angiogenesis
Vascular Repair

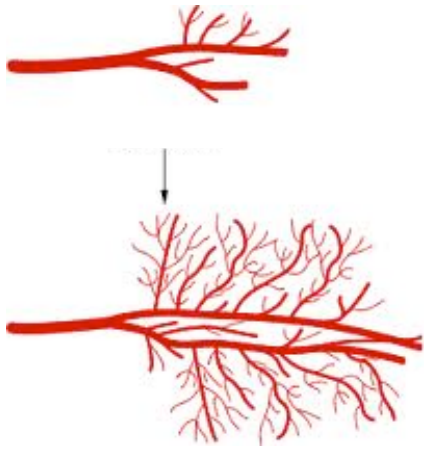
Contemporary ROS and CV System: Major Areas of Influence



Cardiac Function
Hypertrophy

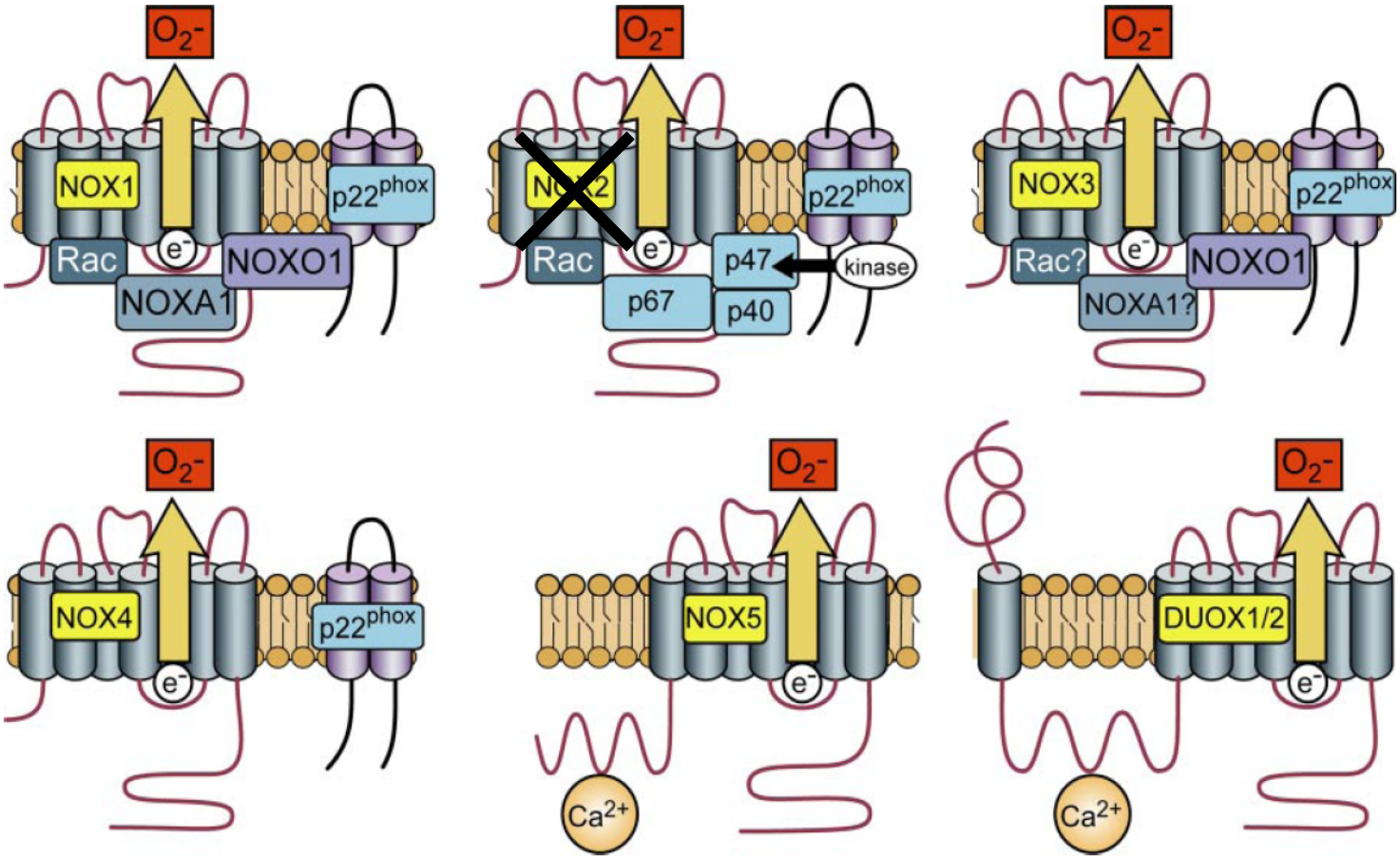


Atherosclerosis
Hypertension



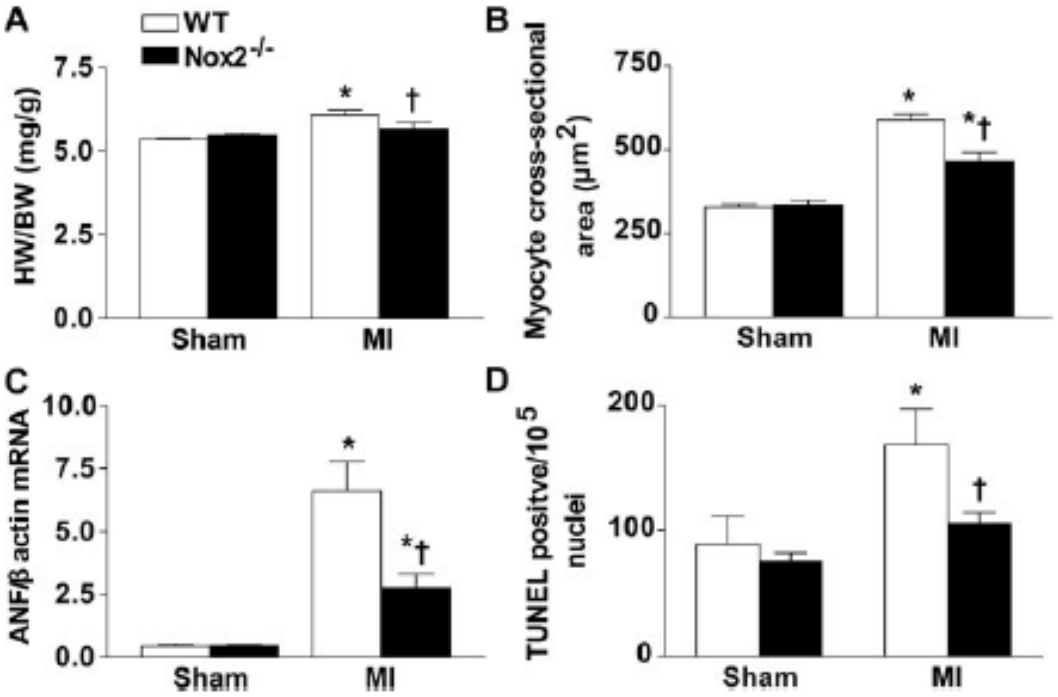
Angiogenesis
Vascular Repair

NADPH Oxidase (Nox) Enzyme Family



Bedard and Krause, *Physiol. Rev.* 2007;87

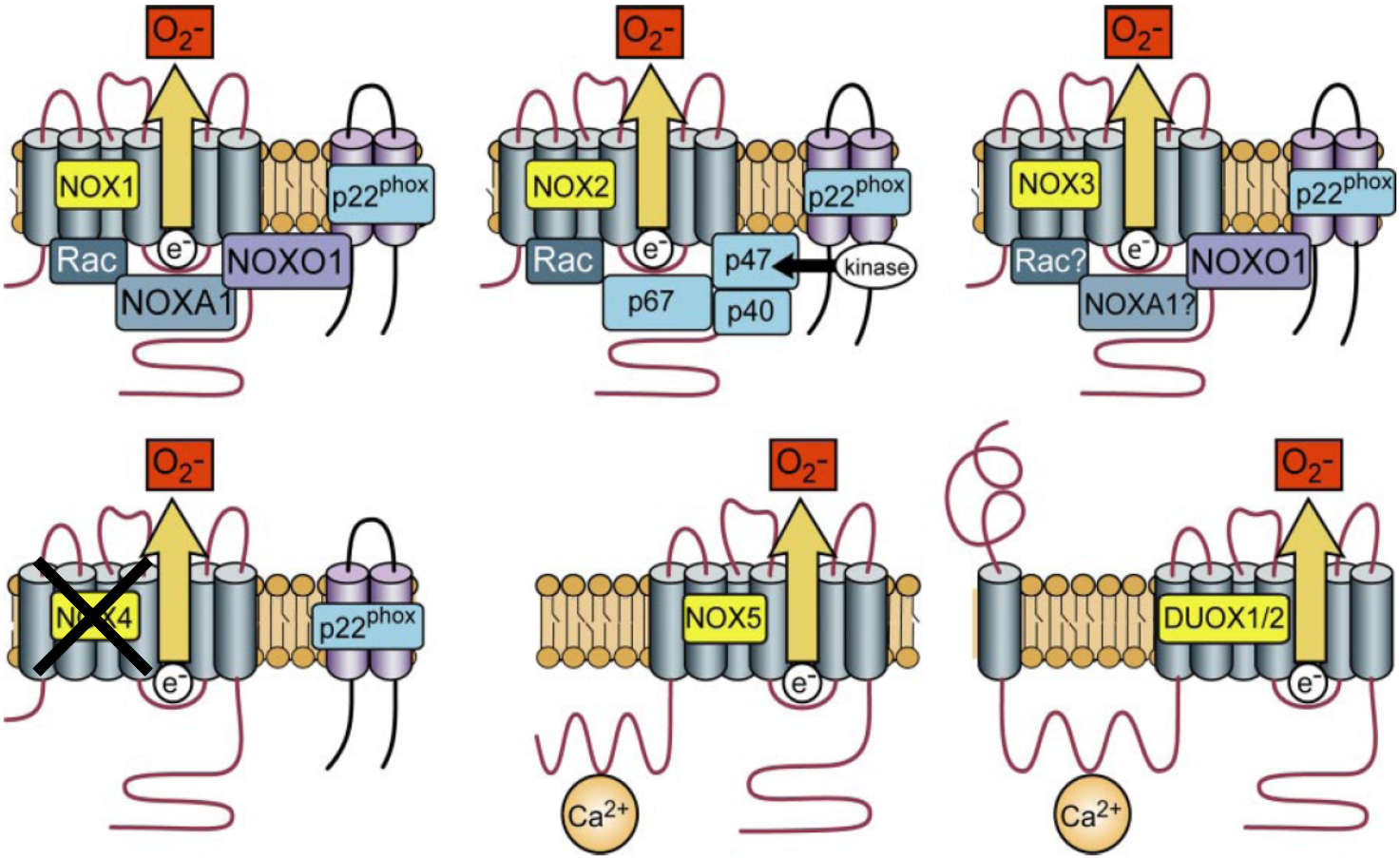
Nox2 Influences Cardiac Remodeling After Myocardial Infarction



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

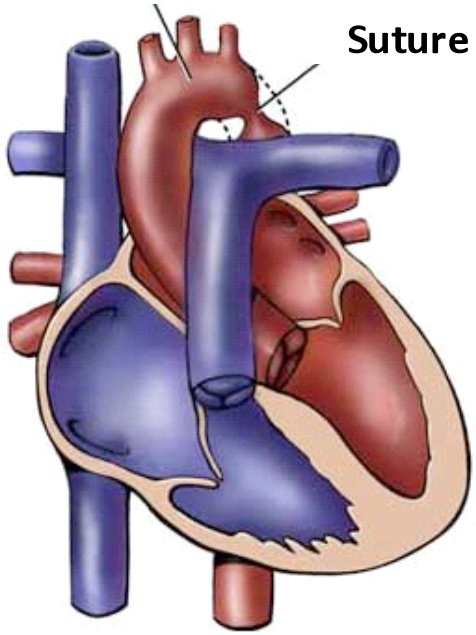
Hypertension. 2008 Feb;51(2):319-25

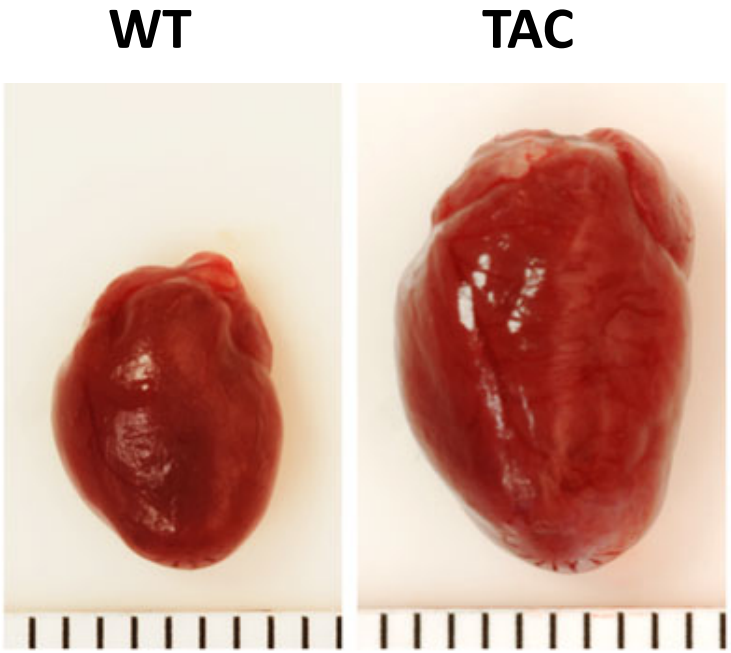
NADPH Oxidase (Nox) Enzyme Family



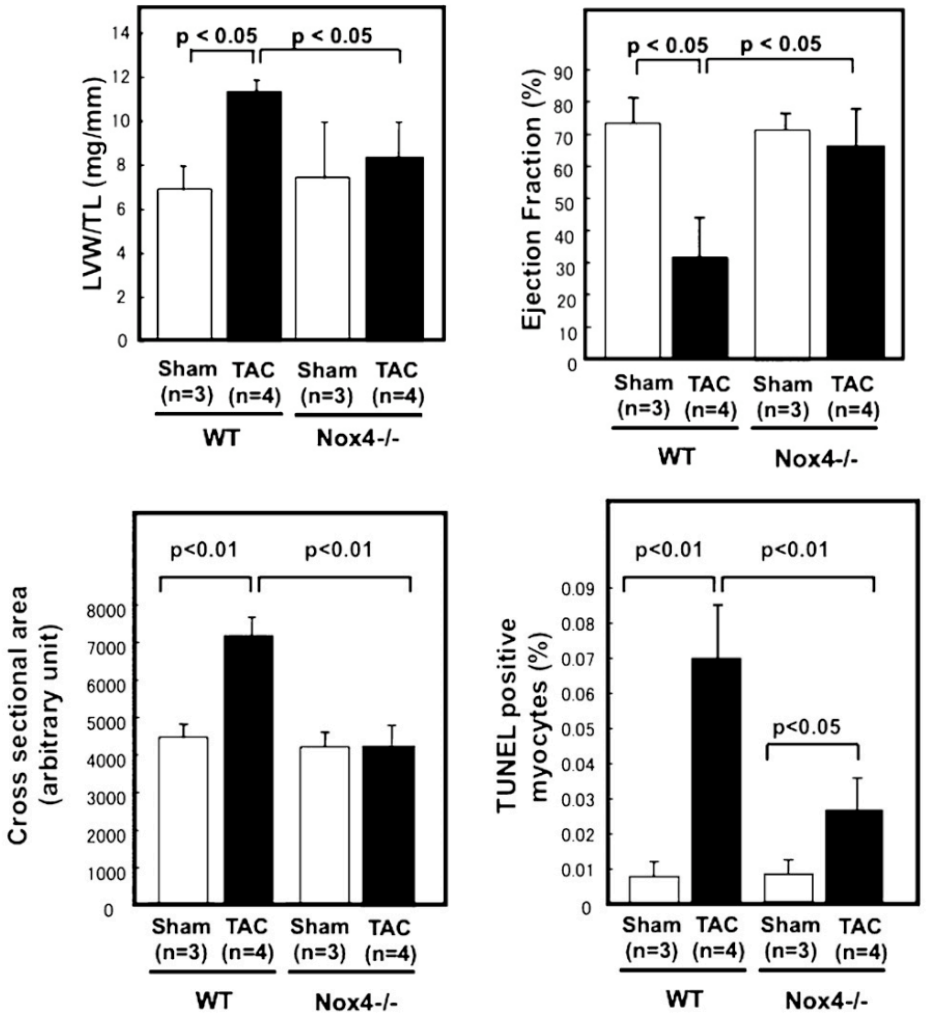
Bedard and Krause, *Physiol. Rev.* 2007;87

Trans Aortic Constriction Model





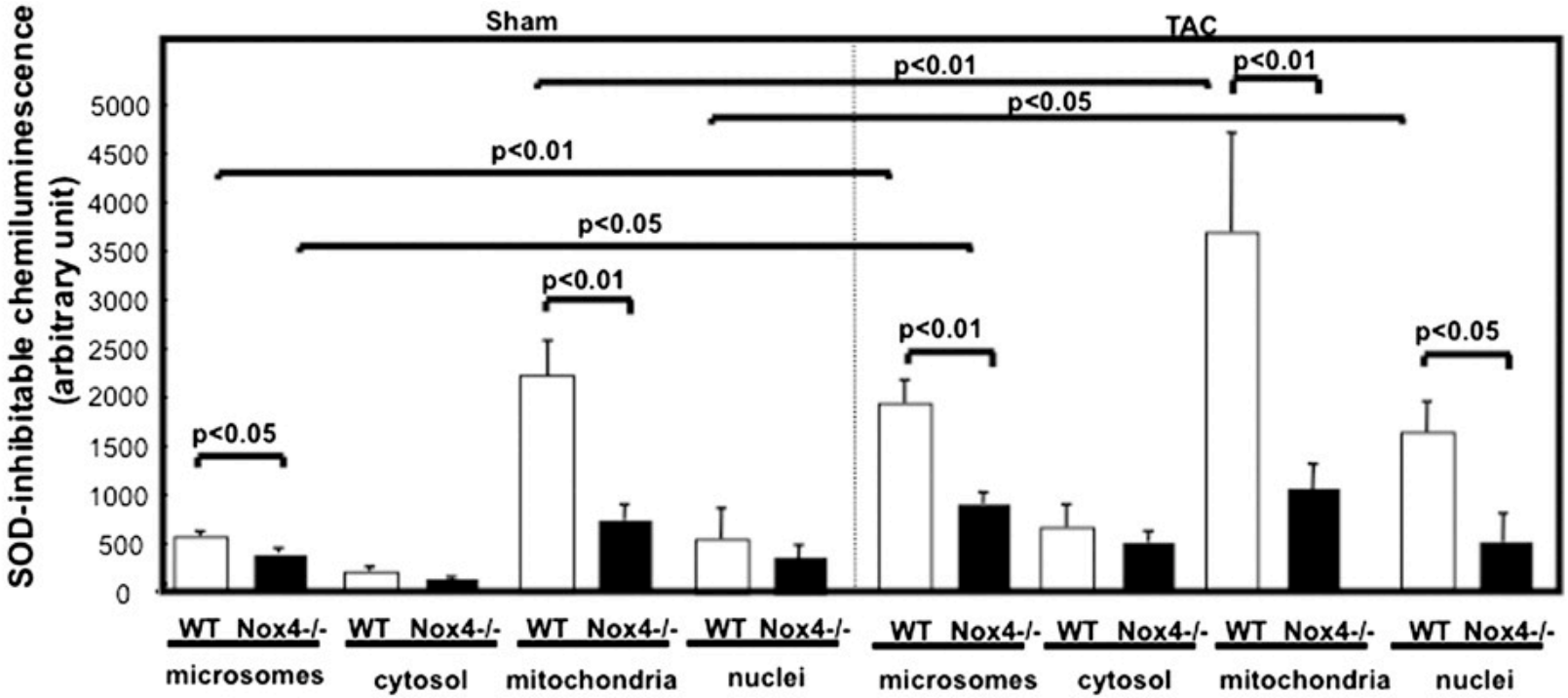
Cardiac Nox4 is Deleterious in Pressure Overload



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

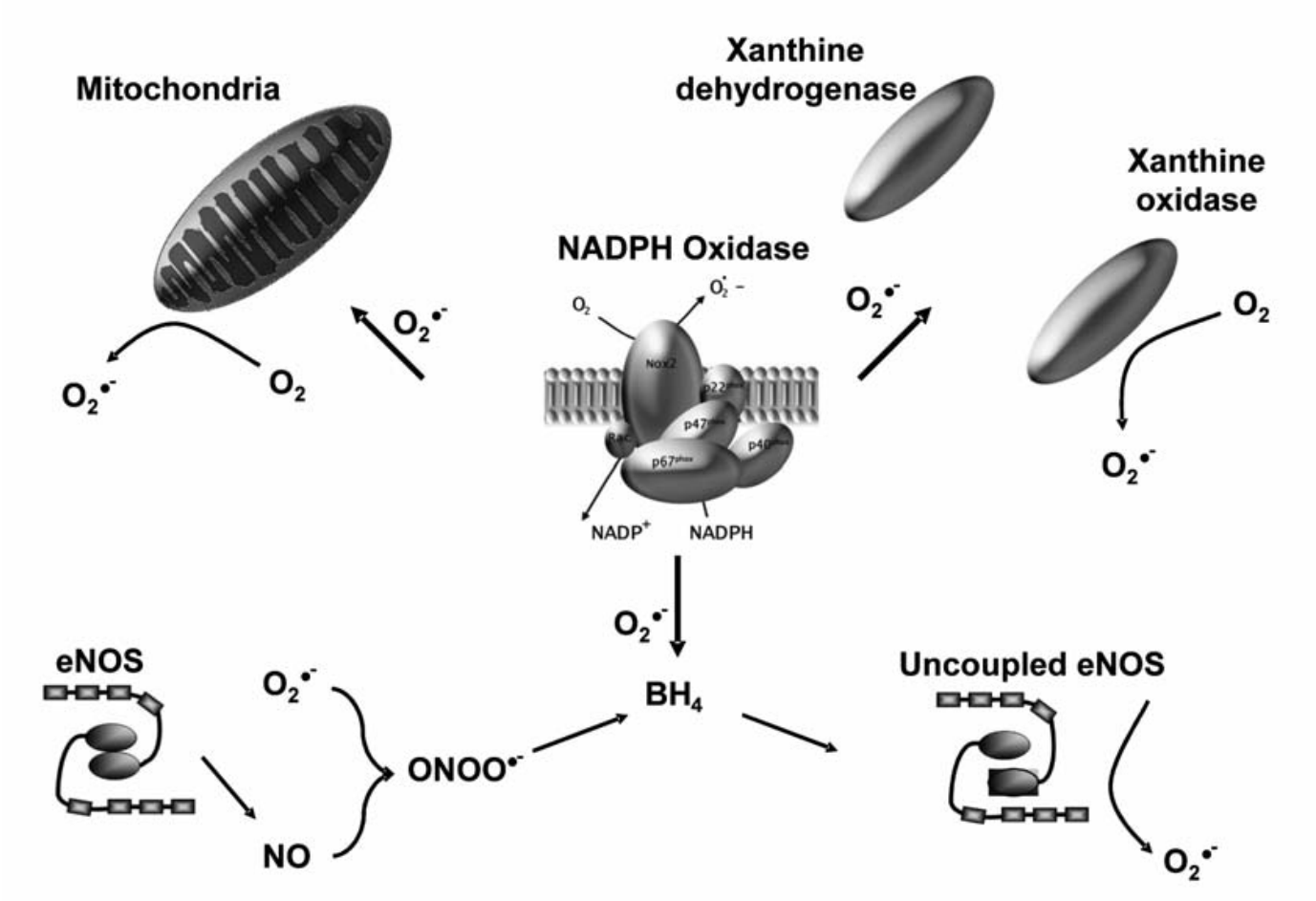
Kuroda J et al. PNAS 2010;107:15565-15570

Nox4 Impacts Multiple ROS Sources



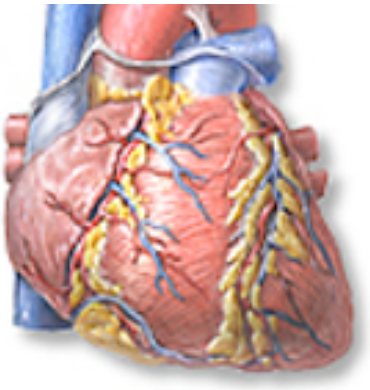
Kuroda J et al. PNAS 2010;107:15565-15570

Interaction of ROS Sources

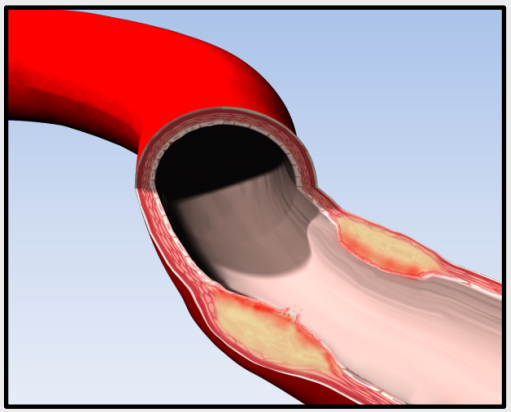


Cave et. al. Antioxid. Redox Signal. 8, 691–728

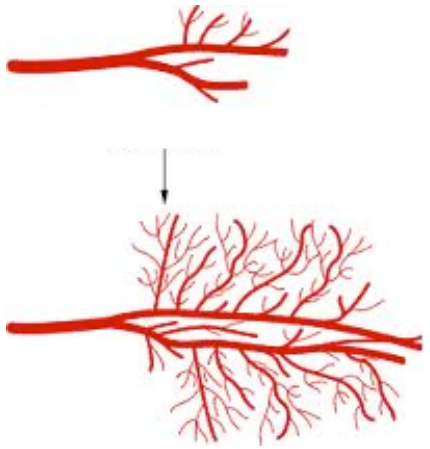
Contemporary ROS and CV System: Major Areas of Influence



Cardiac Function
Hypertrophy

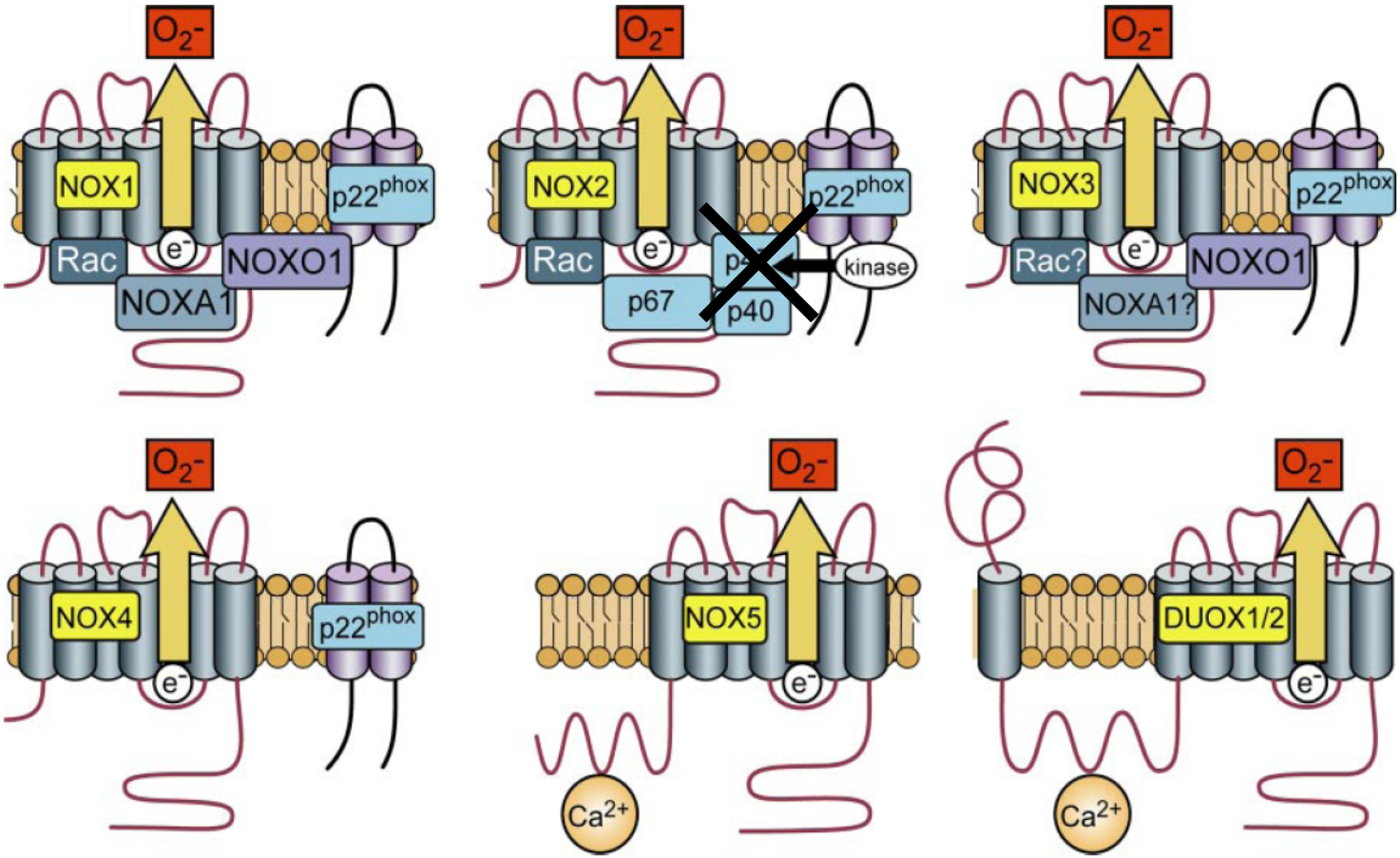


Atherosclerosis
Hypertension



Angiogenesis
Vascular Repair

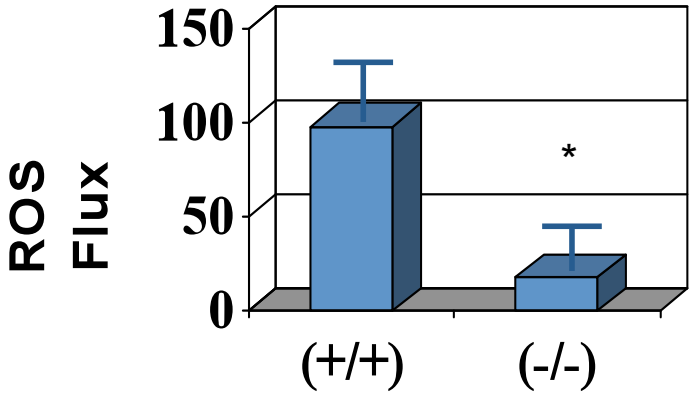
NADPH Oxidase (Nox) Enzyme Family



Bedard and Krause, *Physiol. Rev.* 2007;87

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



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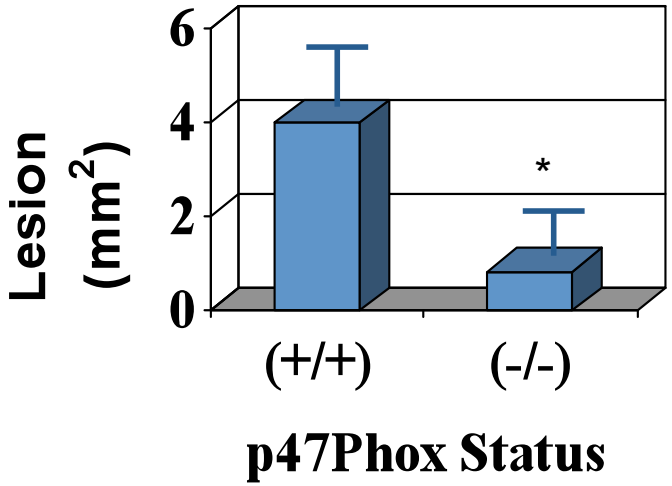
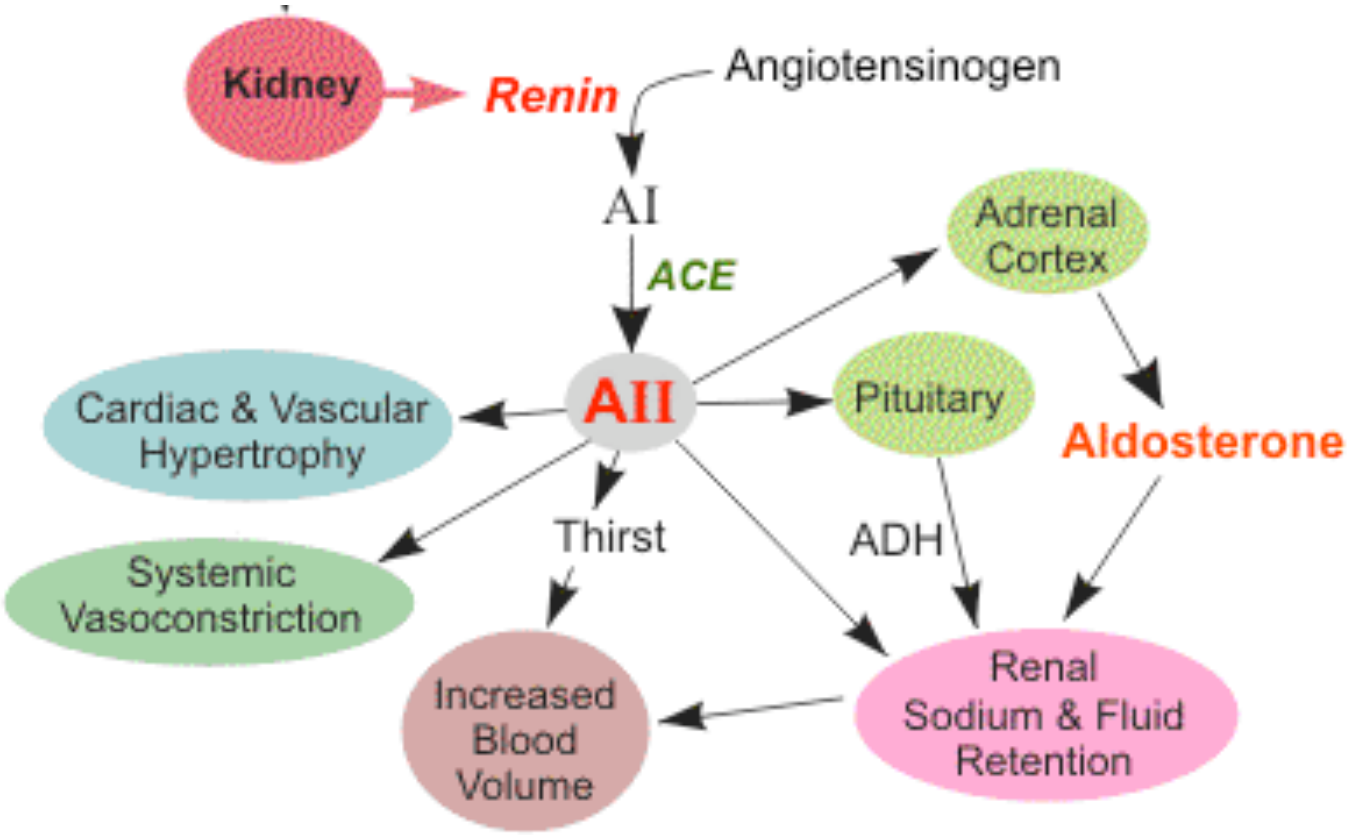


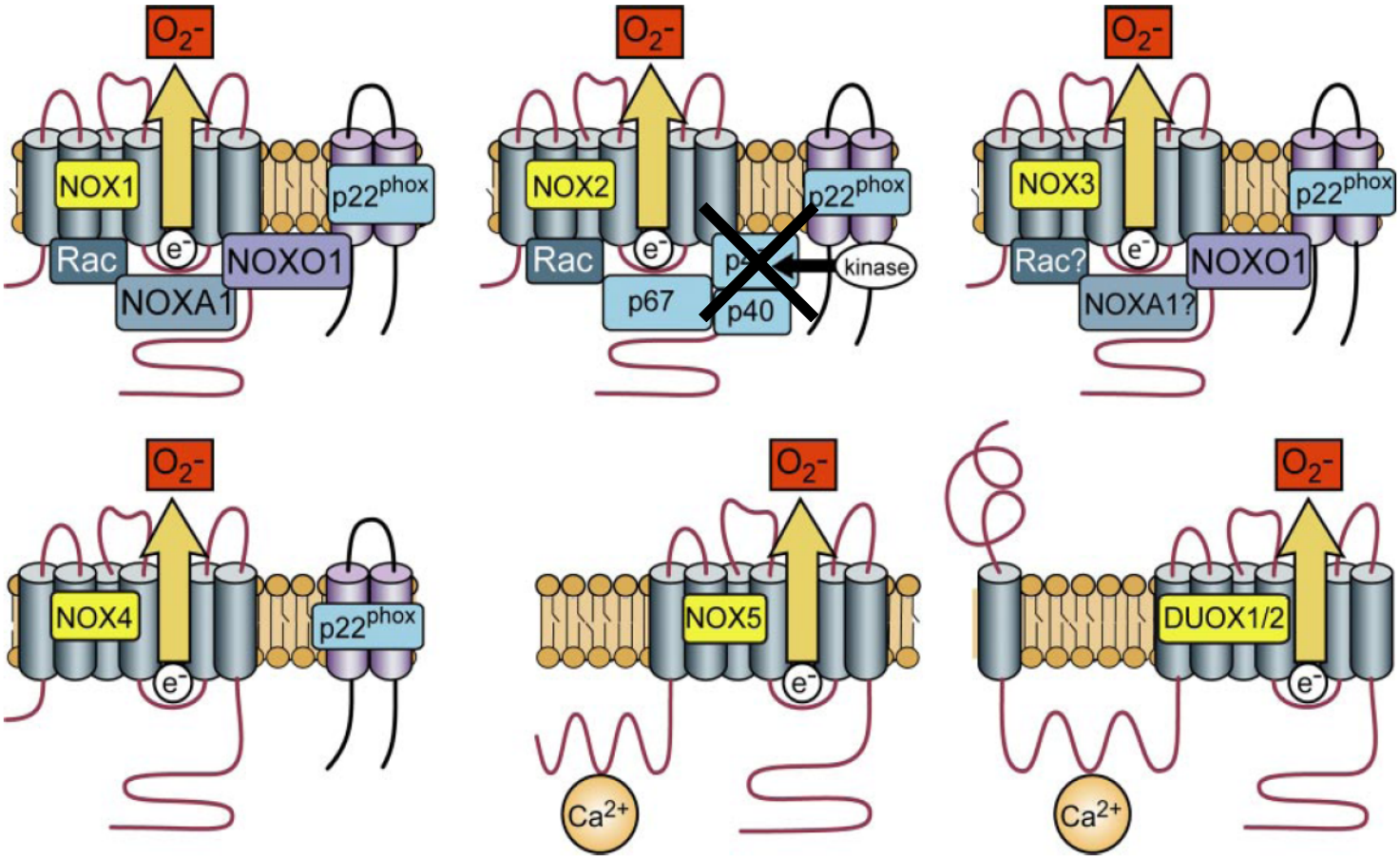
Barry-Lane et al. *J. Clin. Invest.* 2001;108:1513

What about hypertension?

Renin-Angiotensin System

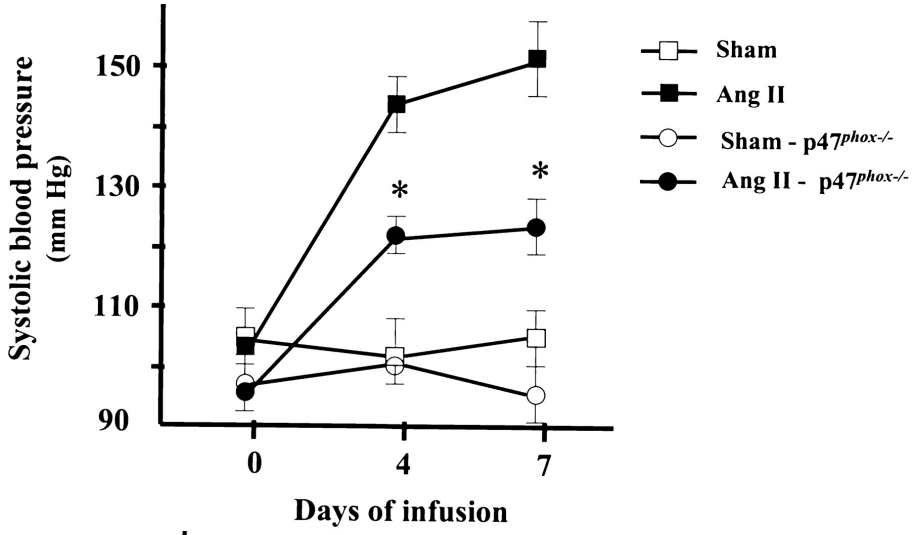


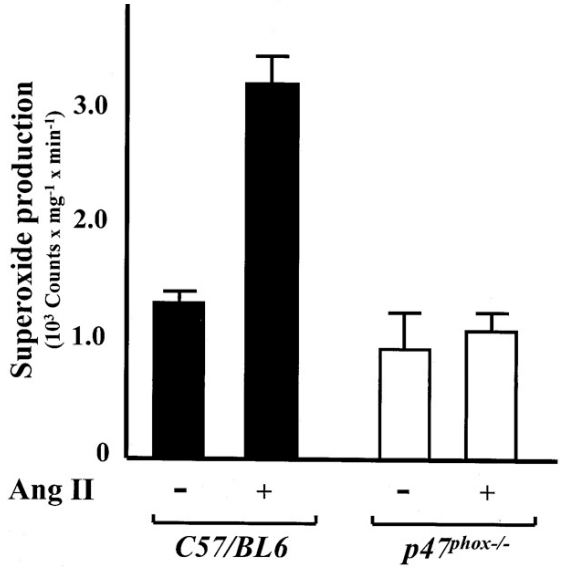
NADPH Oxidase (Nox) Enzyme Family



Bedard and Krause, *Physiol. Rev.* 2007;87

Nox2 and Hypertension



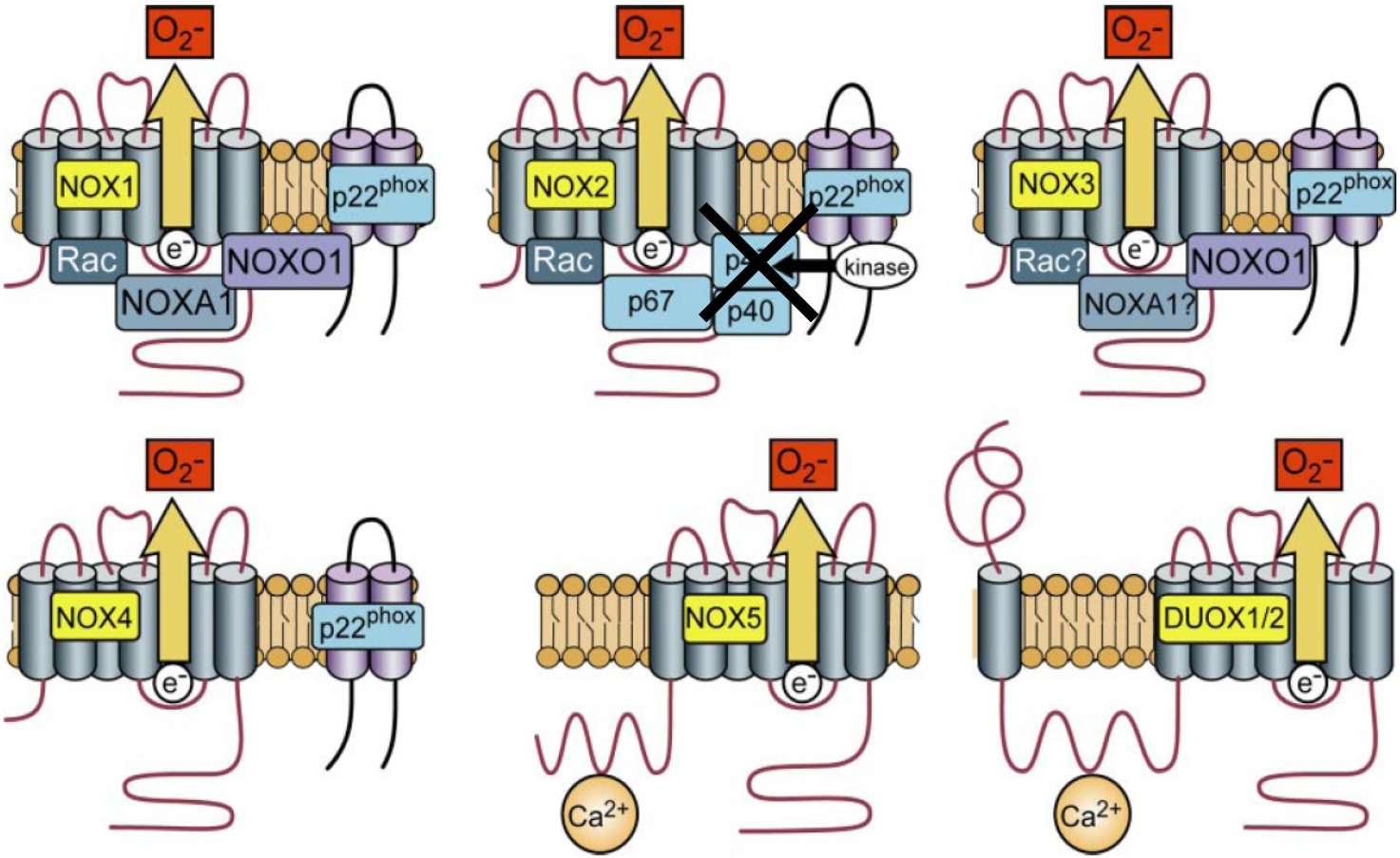


- Less ROS produced from blood vessels
- Less rise in blood pressure
- Less vascular hypertrophy

Landmesser, U. et al. Hypertension 2002;40:511-515

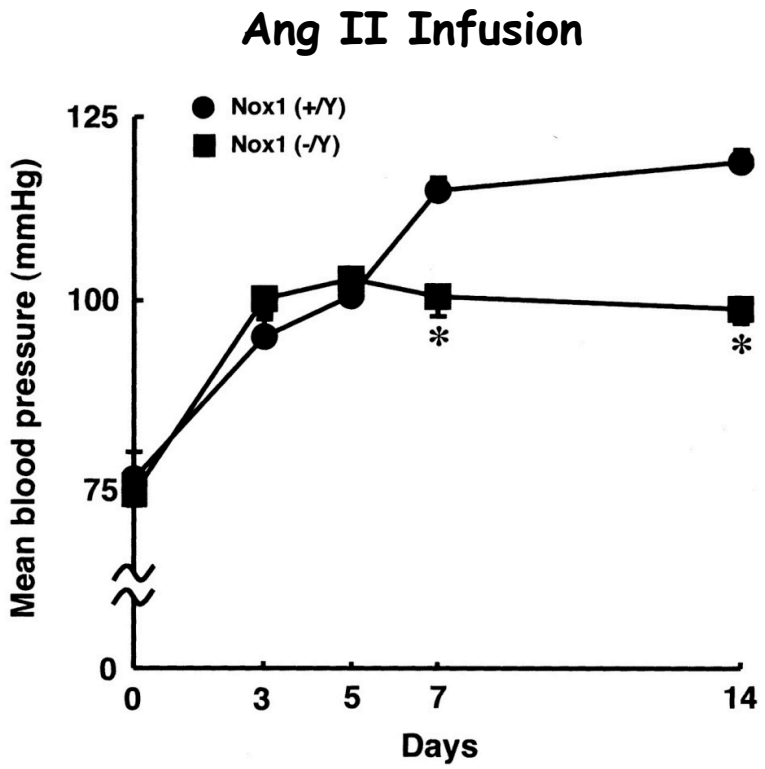
Not all ROS sources are equal!

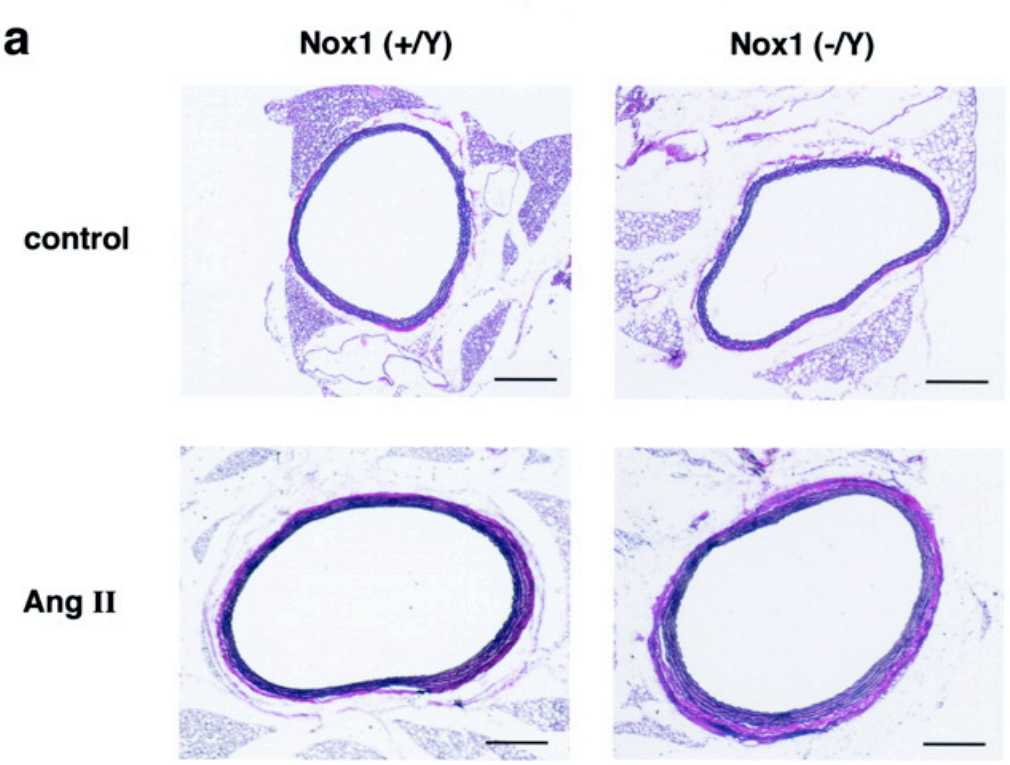
NADPH Oxidase (Nox) Enzyme Family



Bedard and Krause, *Physiol. Rev.* 2007;87

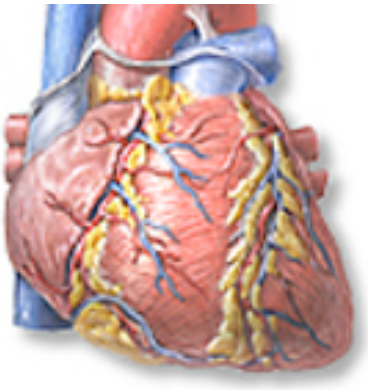
BP and Hypertrophy are Distinct



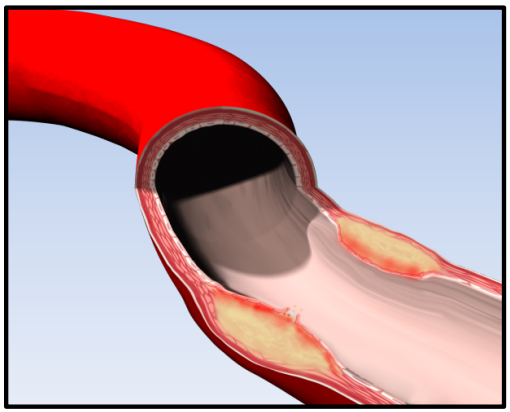


Matsuno, K. et al. Circulation 2005;112:2677-2685

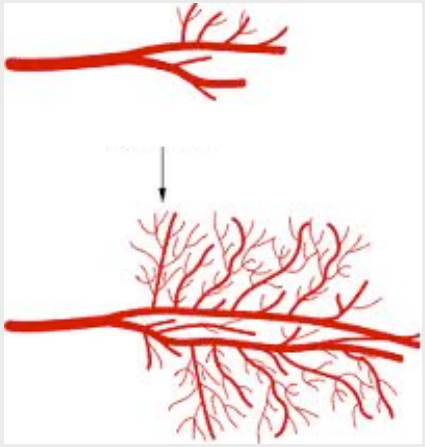
Contemporary ROS and CV System: Major Areas of Influence



Cardiac Function
Hypertrophy

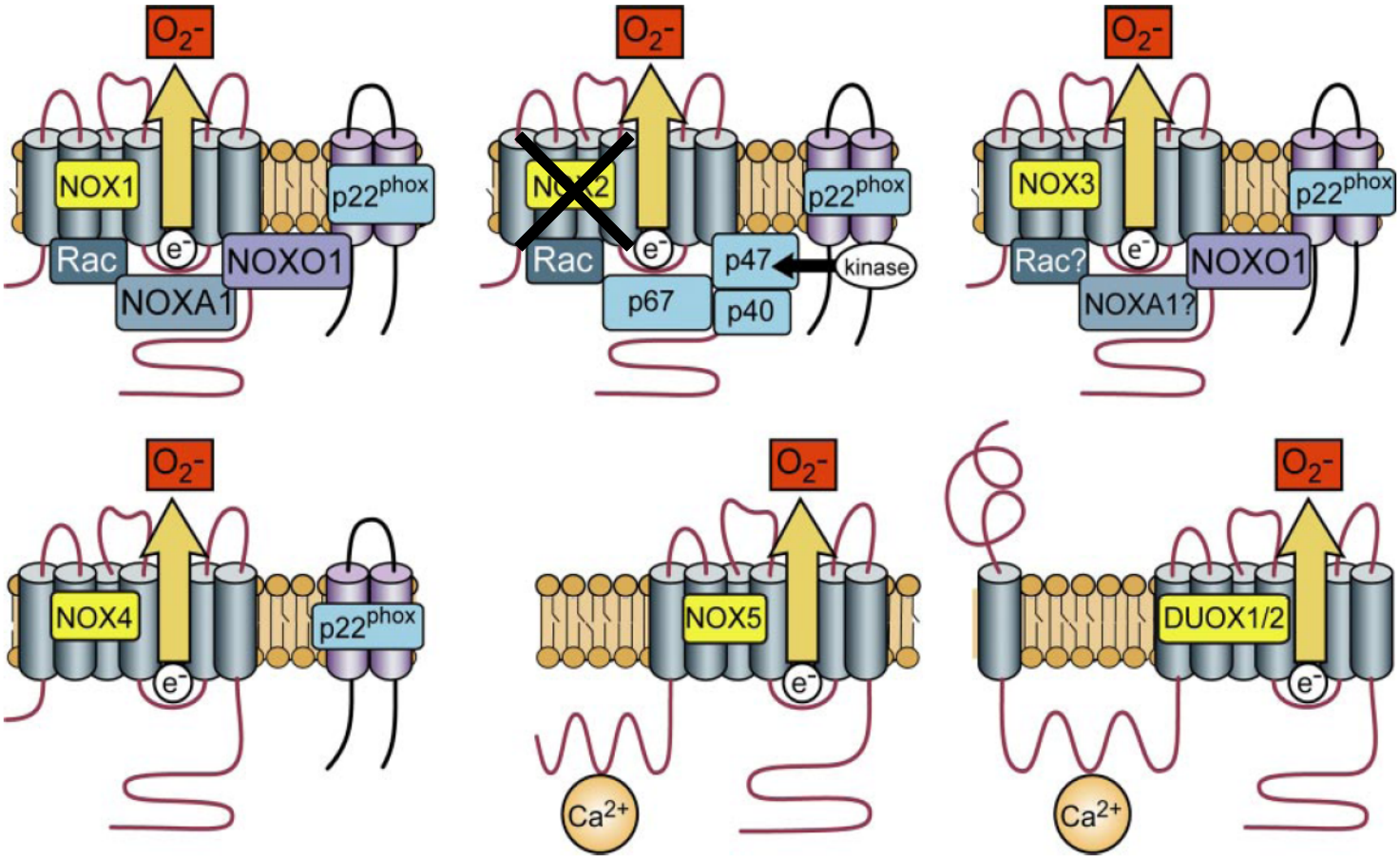


Atherosclerosis
Hypertension



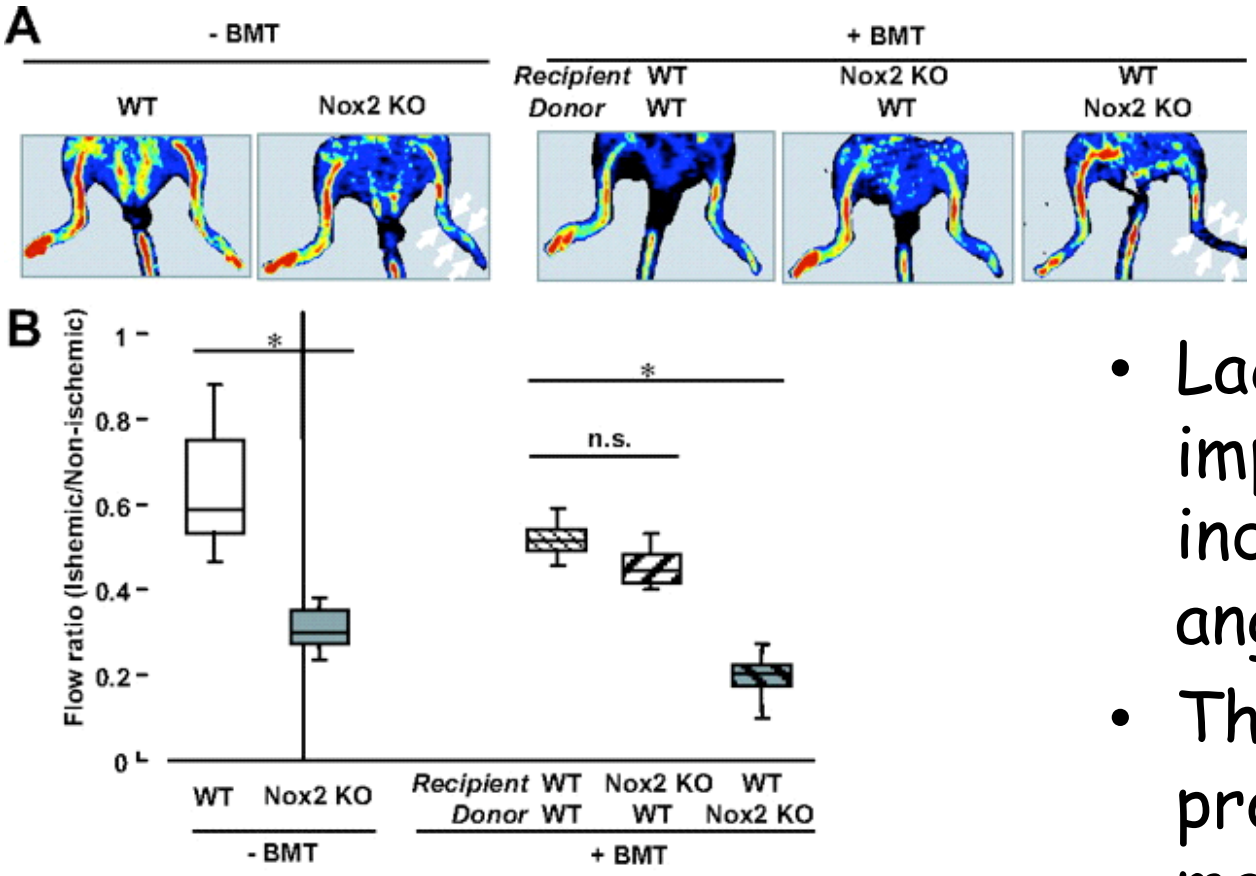
Angiogenesis
Vascular Repair

NADPH Oxidase (Nox) Enzyme Family



Bedard and Krause, *Physiol. Rev.* 2007;87

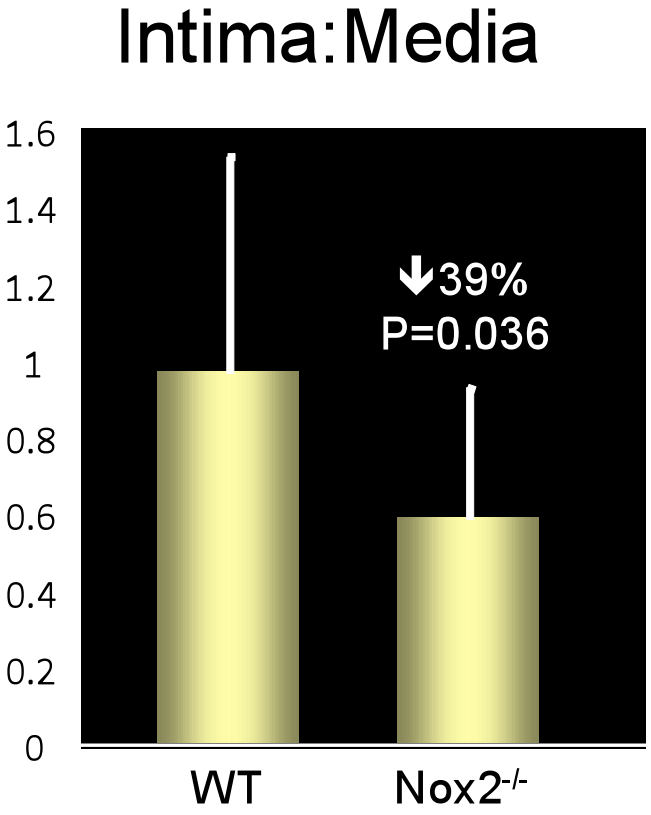
Bone Marrow Nox2 is Important for Ischemia-Induced Angiogenesis

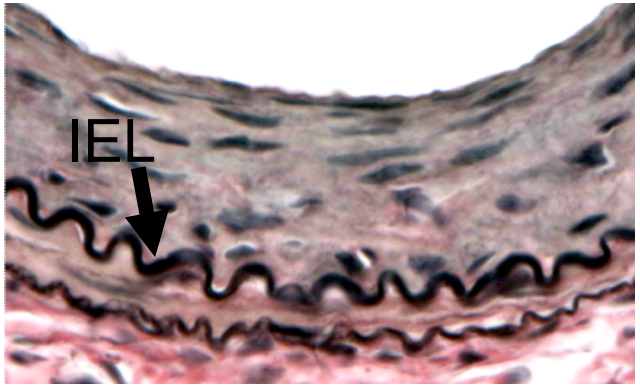


- Lack of Nox2 impairs ischemia-induced angiogenesis
- This effect is most prominent in bone marrow

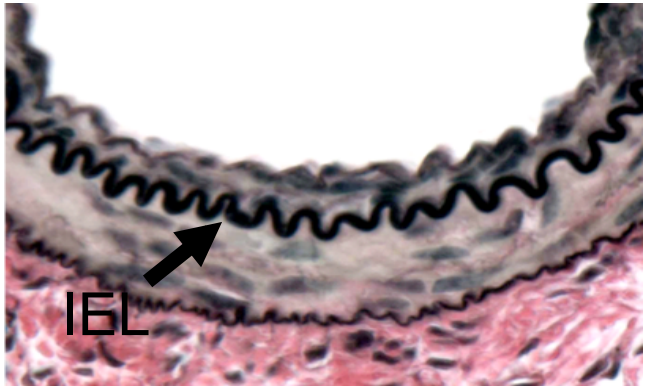
Urao, N. et al. Circ Res 2008;103:212-220

Nox2 Modifies Arterial Injury





Wild-type, 28d

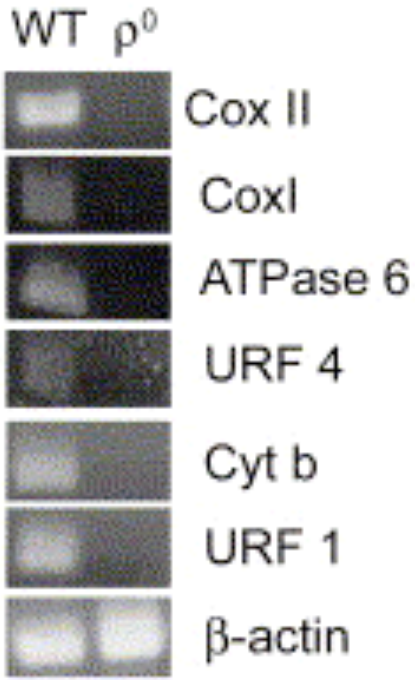


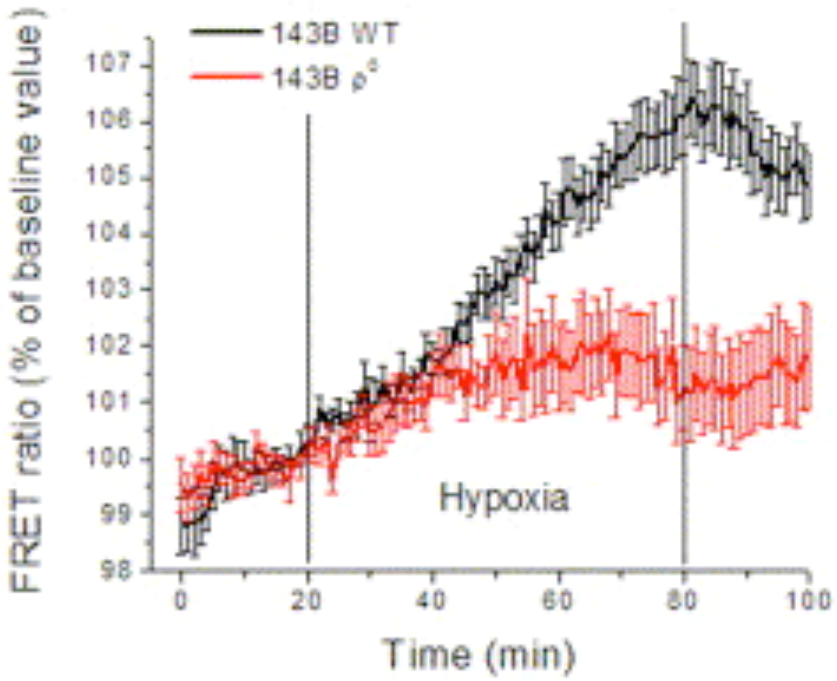
Nox2$^{-/-}$, 28d

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)