Dr. Cuihua Zhang's Memorial Lecture

Redox Regulation of Endothelial Cell Phenotypes -Role of AMP-activated Protein Kinase

Ming-Hui Zou, MD PhD

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Cuihua Zhang MD PhD
(1962-2011)

November 2007 Chicago CADA meeting

Cuihua Zhang, MD PhD

- Jin Zhou Medical College, MD, PhD from Chinese Academy of Medical Science and Peking Union Medical College, PhD
- Research Fellow, University of San Paulo, Brazil ; Postdoctoral fellow, Department of Medical Physiology, College of Medicine, Texas A&M University
- Assistant Research Scientist, Department of Medical Physiology, College of Medicine, Texas A&M University
- Assistant Professor, Departments of Anesthesiology, Surgery and Physiology, LSU Health Sciences Center, School of Medicine, New Orleans, LA
- Assistant Professor, Department of Veterinary Physiology and Pharmacology, Texas A&M University, College Station, TX
- Associate Professor (with tenure), Departments of Internal Medicine, Medical Pharmacology & Physiology and Nutritional Sciences, University of Missouri
- Recipient of Werner Risau New Investigator Award in Vascular Biology from ATVB ; Recipient of American Physiology Society CV Section Young Investigator Award
- Research funded by the National Institutes of Health, American Heart Association and Pfizer

10 Publications in 2011

- Li J, Zhang H, **Zhang C.** Role of inflammation in the regulation of coronary blood flow in ischemia and reperfusion: Mechanisms and therapeutic implications. J Mol Cell Cardiol. 2011
- Zhang H, Potter BJ, Cao JM, **Zhang C.** Interferon-gamma induced adipose tissue inflammation is linked to endothelial dysfunction in type 2 diabetic mice. Basic Res Cardiol. 2011 Aug 9.
- Zhang H, Wang Y, Zhang J, Potter BJ, Sowers JR, **Zhang C.** Bariatric surgery reduces visceral adipose inflammation and improves endothelial function in type 2 diabetic mice. Arterioscler Thromb Vasc Biol. 2011 Sep;31(9):2063-9. Epub 2011 Jun 16.
- Lee S, Park Y, Dellsperger KC, **Zhang C.** Exercise training improves endothelial function via adiponectin-dependent and independent pathways in type 2 diabetic mice. Am J Physiol Heart Circ Physiol. 2011 Aug;301(2):H306-14.
- Wu J, Li J, Zhang N, **Zhang C.** Stem cell-based therapies in ischemic heart diseases: a focus on aspects of microcirculation and inflammation. Basic Res Cardiol. 2011 May;106(3):317-24.
- **Zhang C.** Cardiovascular physiology at the bench for application in the clinic. World J Cardiol. 2011 Feb 26;3(2):59-64.
- Gao X, Martinez-Lemus LA, **Zhang C.** Endothelium-derived hyperpolarizing factor and diabetes. World J Cardiol. 2011 Jan 26;3(1):25-31.
- Lee S, Park Y, Zuidema MY, Hannink M, **Zhang C.** Effects of interventions on oxidative stress and inflammation of cardiovascular diseases. World J Cardiol. 2011 Jan 26;3(1):18-24.
- Ungvari Z, Bailey-Downs L, Gautam T, Jimenez R, Losonczy G, **Zhang C,** Ballabh P, Recchia FA, Wilkerson DC, Sonntag WE, Pearson K, de Cabo R, Csizar A. Adaptive induction of NF-E2-related factor-2-driven antioxidant genes in endothelial cells in response to hyperglycemia. Am J Physiol Heart Circ Physiol. 2011 Apr;300(4):H1133-40.


2009 9 14

J Mol Cell Cardiol. 2011 Sep 5. [Epub ahead of print]

Role of inflammation in the regulation of coronary blood flow in ischemia and reperfusion: Mechanisms and therapeutic implications

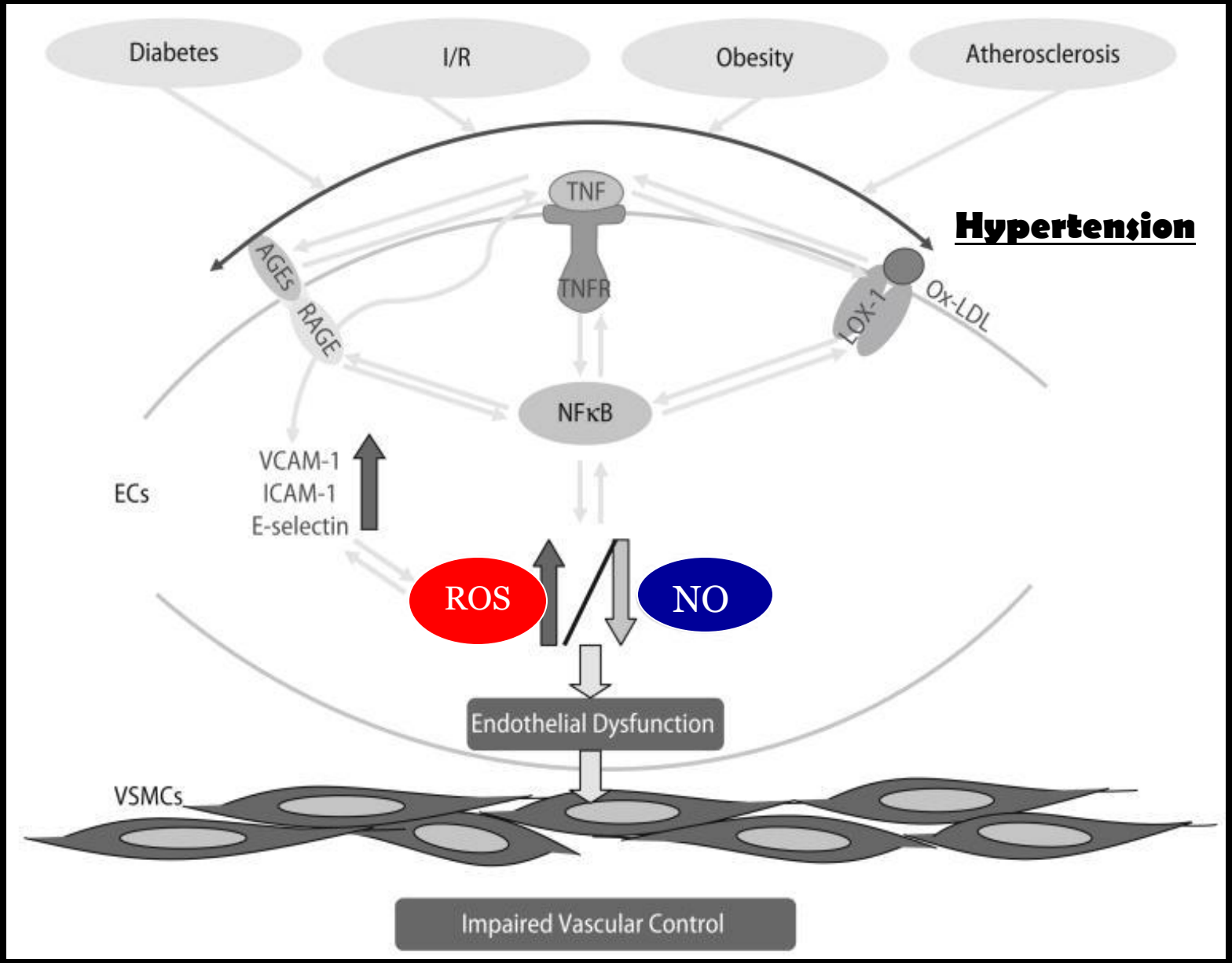
Jun Li[1], Hanrui Zhang[1], Cuihua Zhang,

Received 18 May 2011; revised 14 August 2011; Accepted 29 August 2011. Available online 5 September 2011.

Main Research Contributions: TNF alpha, Oxidative Stress, and endothelial dysfunction in coronary arteries

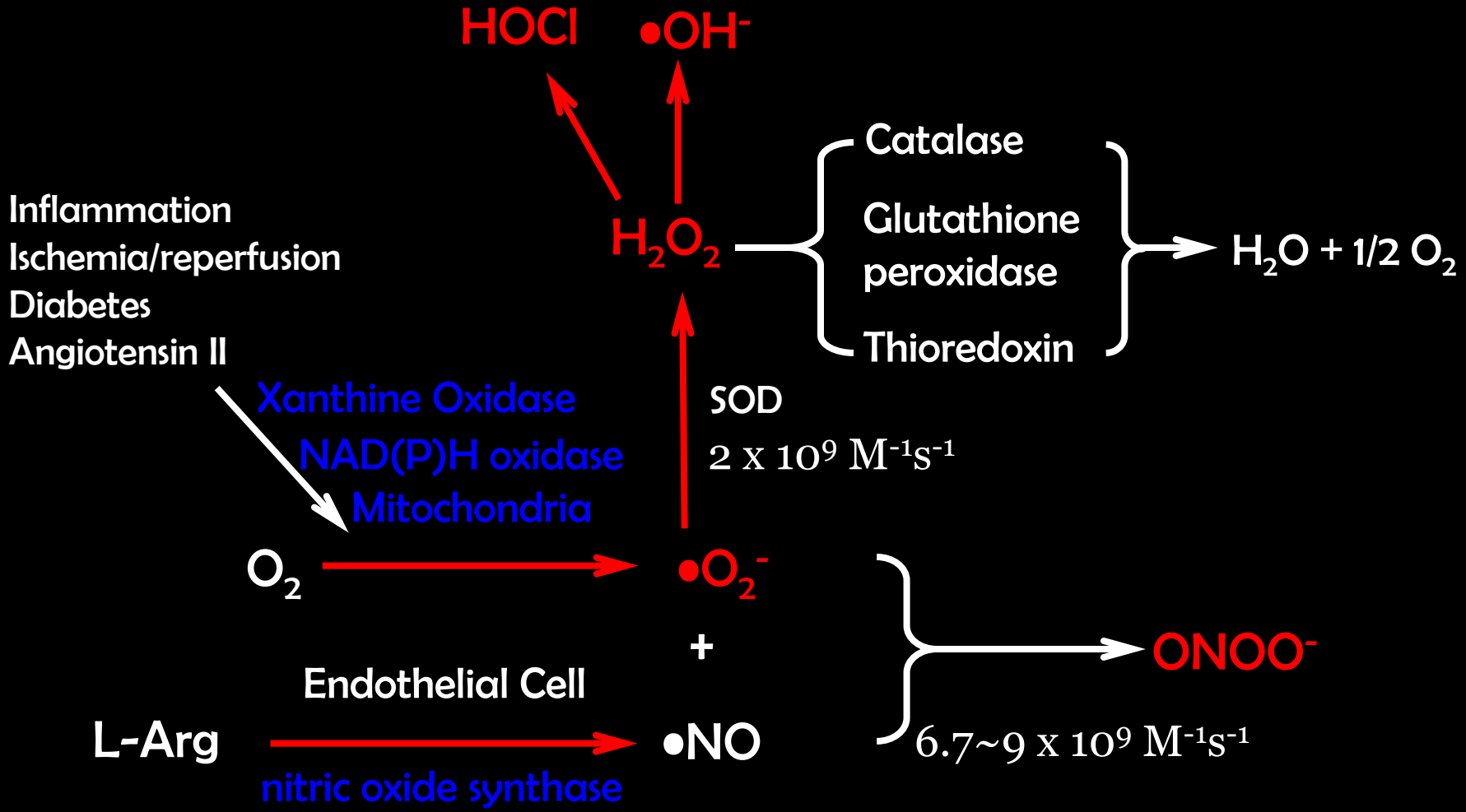
(total 36 out of 64 papers in Pubmed)

- TNF alpha increases arginase in diabetes (Circ Res. 2006 Jul 7;99(1):69-77)
- TNF alpha induces endothelial dysfunction in db/db mice (Circulation. 2007 Jan 16;115(2):245-54.)
- TNF alpha in endothelial dysfunction in ischemia-reperfusion injury;
- TNF alpha in pre-diabetic states
- TNF alpha increases arginase in hypertension

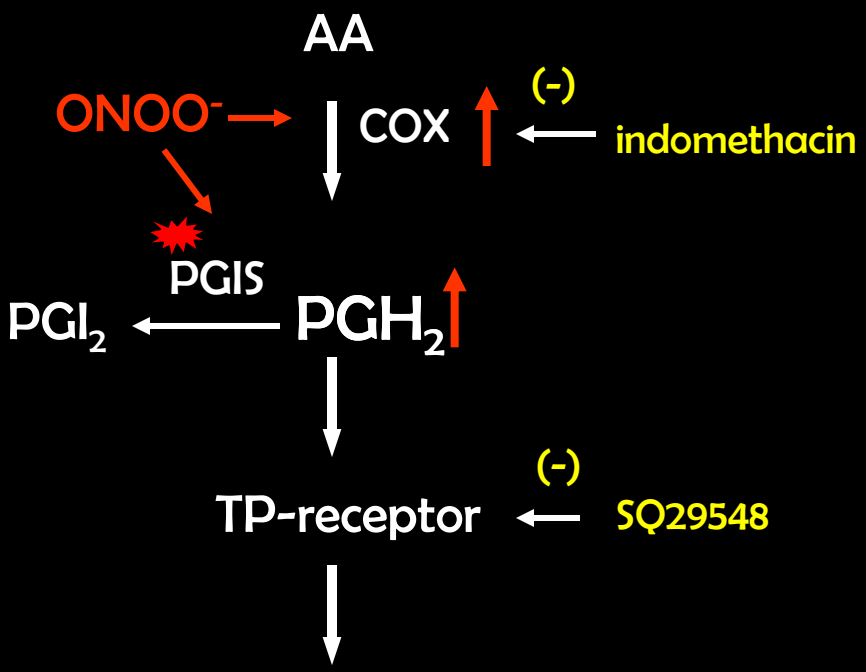


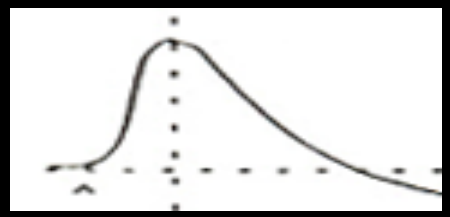
From Cuihua Zhang, Basic Res Cardiol. 2008 Sep;103(5):398-406.

ROS and RNS in Endothelial Cells

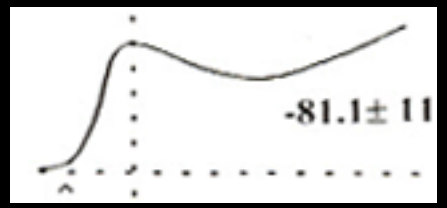


Inactivation of PGIS by peroxynitrite activates thromboxane receptor in isolated bovine coronary arteries

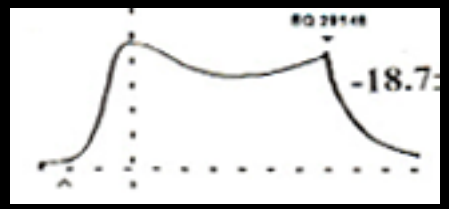




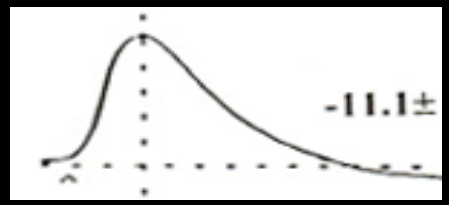
Control



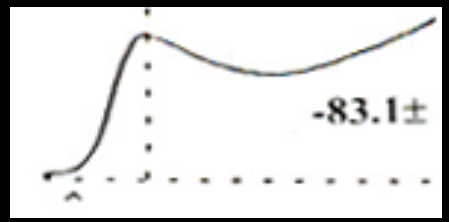
ONOO⁻



ONOO⁻/SQ29548

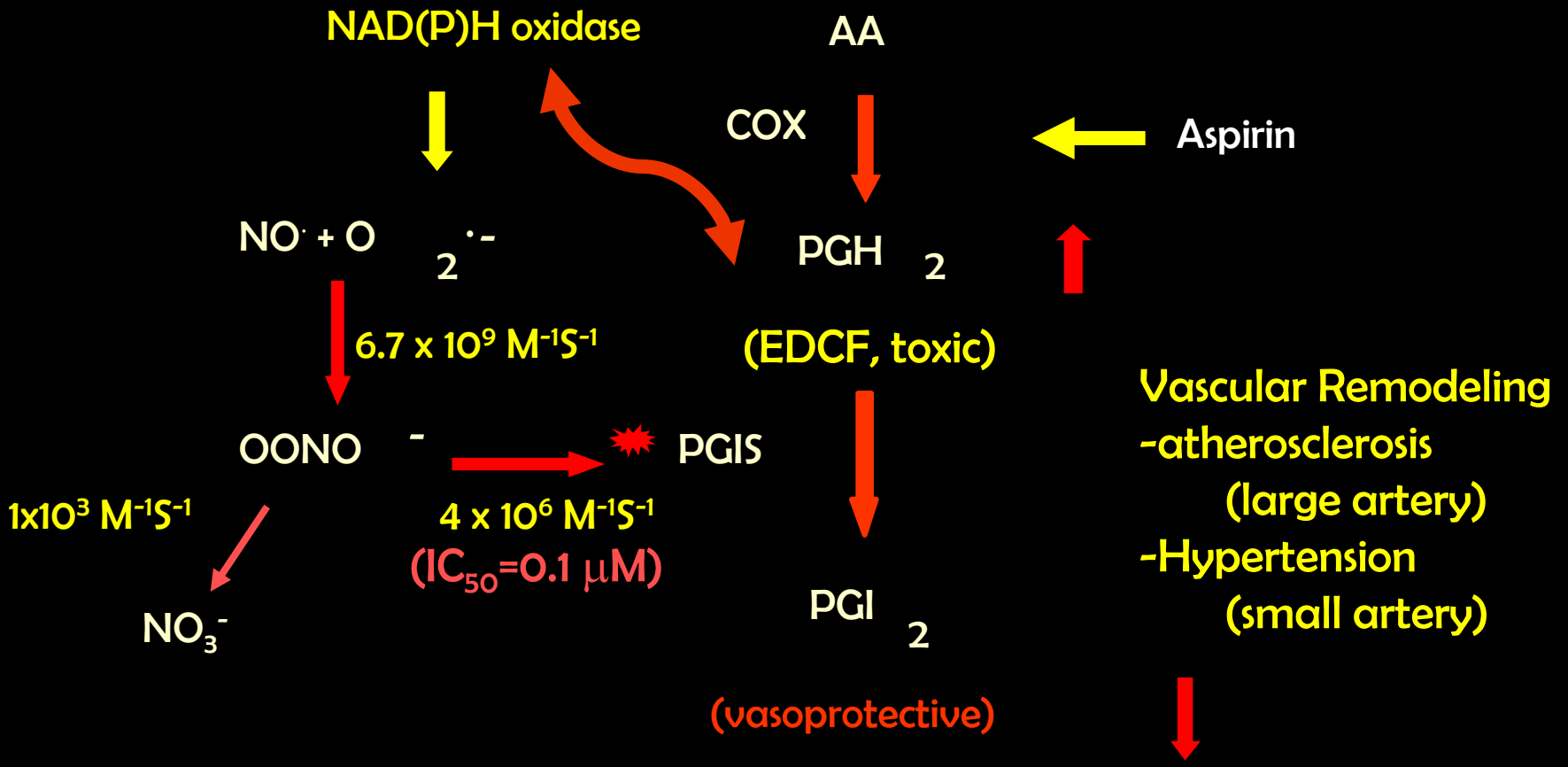


ONOO⁻/Indo



ONOO⁻/CGS13040

RNS and Prostacyclin Synthase (PGIS) Inhibition and Nitration



Original Article

Endothelial Nitric Oxide Synthase–Dependent Tyrosine Nitration of Prostacyclin Synthase in Diabetes In Vivo

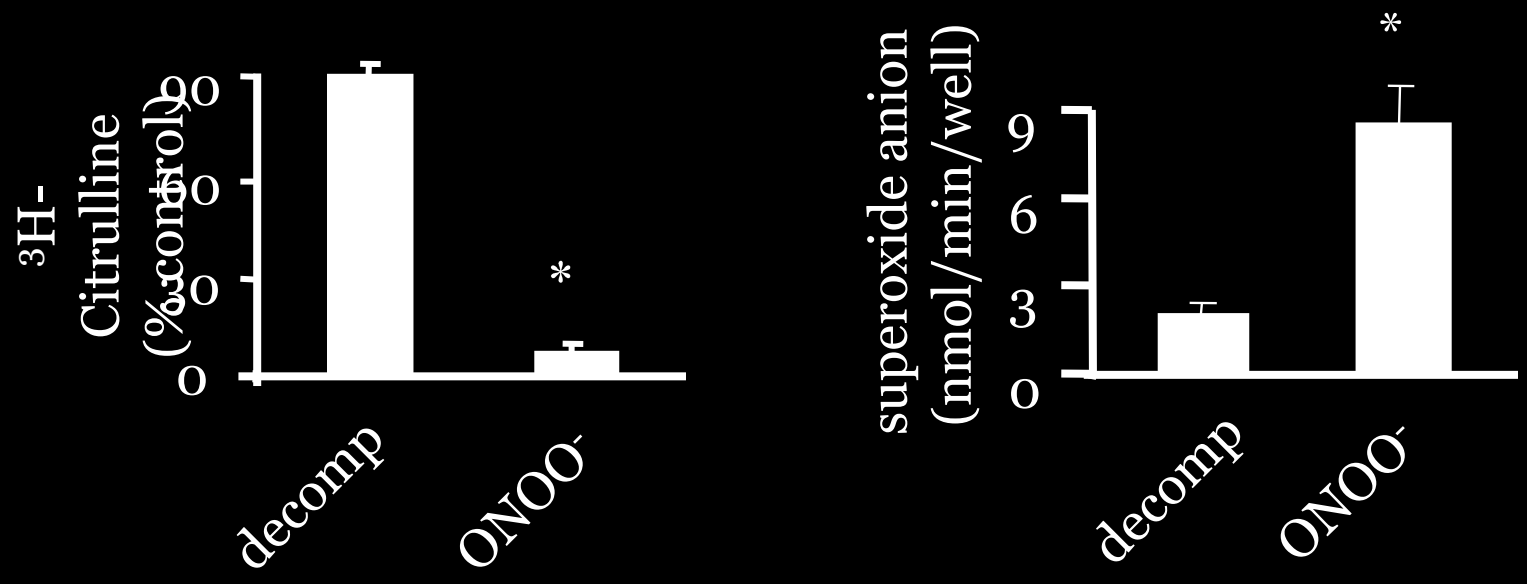
Hong Nie,[1] Ji-liang Wu,[2] Miao Zhang,[3] Jian Xu,[2] and Ming-Hui Zou[2]

There is evidence that reactive nitrogen species are implicated in diabetic vascular complications, but their sources and targets remain largely unidentified. In the present study, we aimed to study the roles of endothelial nitric oxide synthase (eNOS) in diabetes. Exposure of isolated bovine coronary arteries to high glucose (30 mmol/l D-glucose) but not to osmotic control mannitol (30 mmol/l) switched angiotensin II–stimulated prostacyclin (PGI_2)-dependent relaxation into a persistent vasoconstriction

from diabetic patients, as evidenced by increased release of reactive oxygen species, decreased nitric oxide (NO) bioactivity, decreased release of prostacyclin (PGI_2), and enhanced endothelial production of vasoconstrictor thromboxane (Tx)A_2/prostaglandin (PG)H_2 in early stages of diabetes (1–3). The net effect of endothelial dysfunction is vascular damage, which is responsible for complications in both types of diabetes.

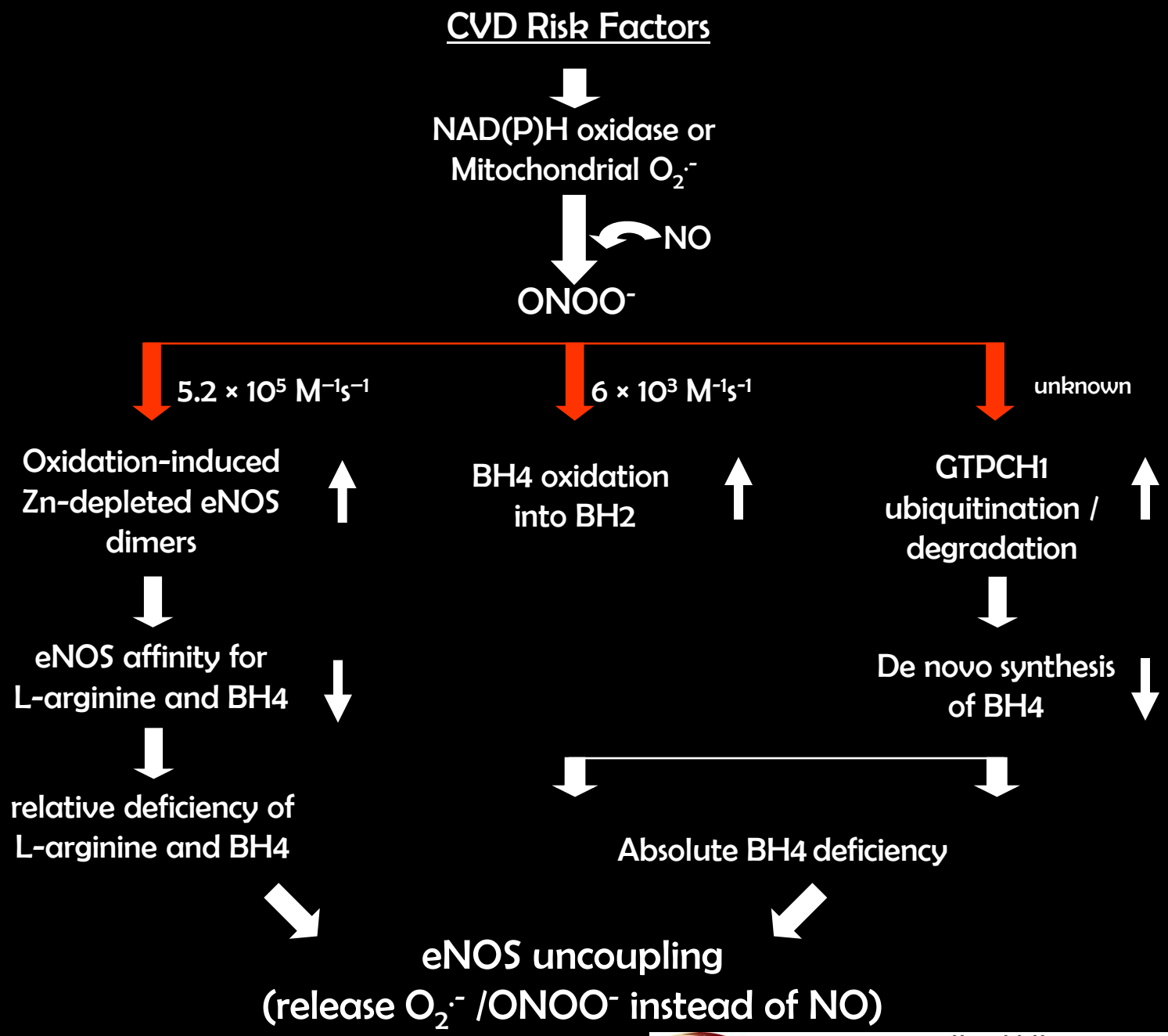
Nie, et al., Diabetes 2006

ONOO$^-$ Causes eNOS Uncoupling (more $O_2^{\cdot -}$ and less NO) in Endothelial Cells

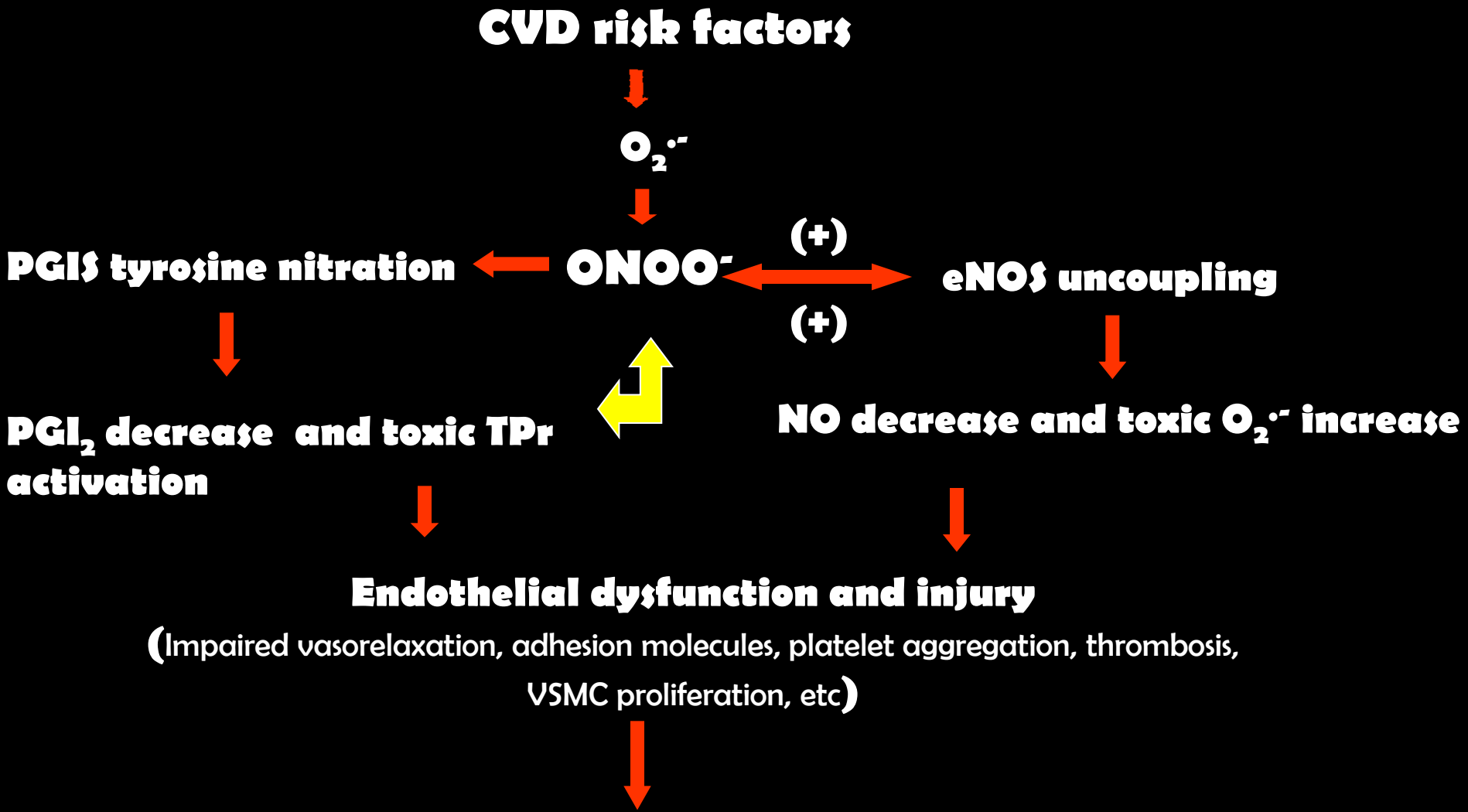


Zou et al. J. Biol. Chem. 277:32552-7, 2002

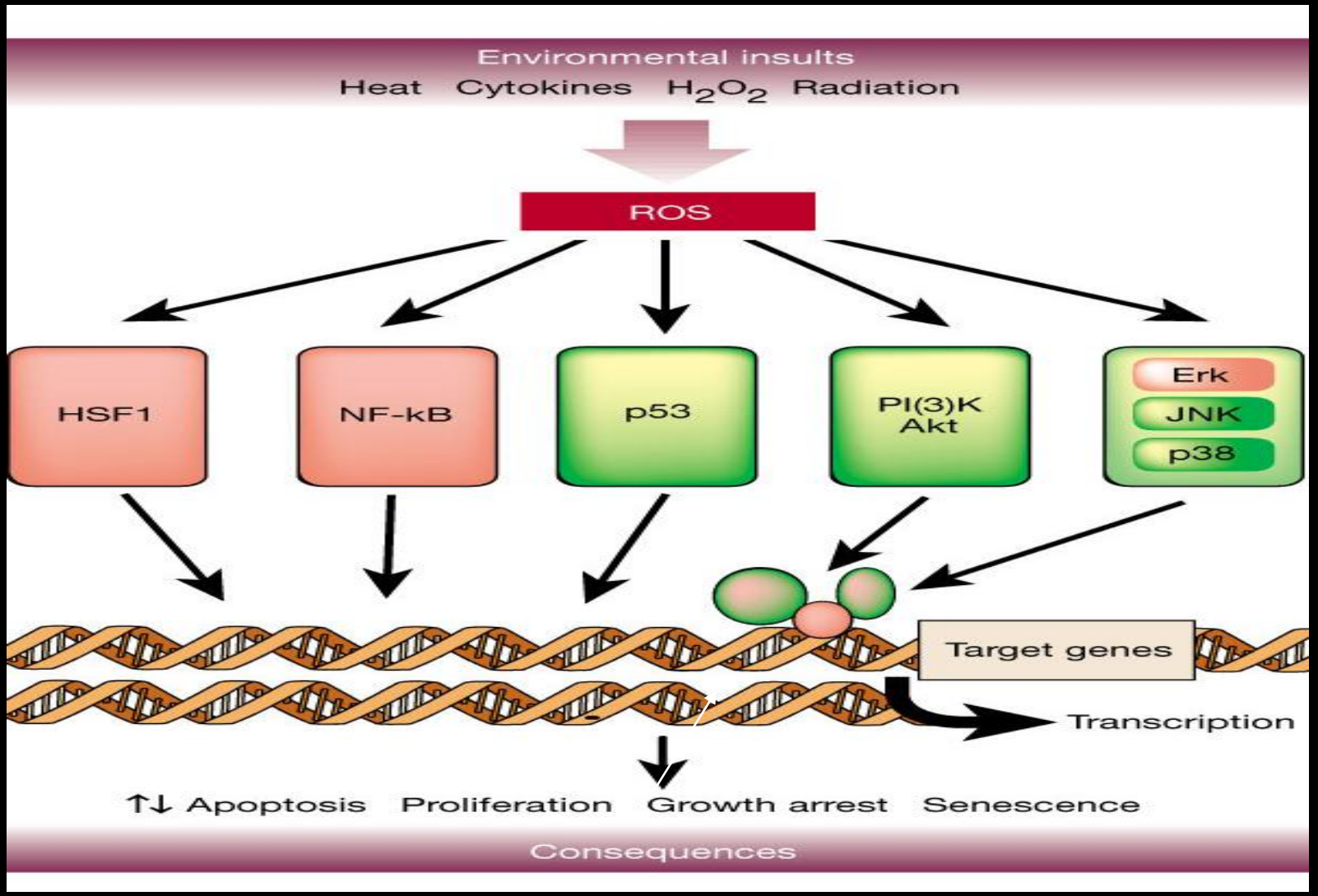
How does eNOS become a source of oxidative stress?



RNS and Endothelial Dysfunction

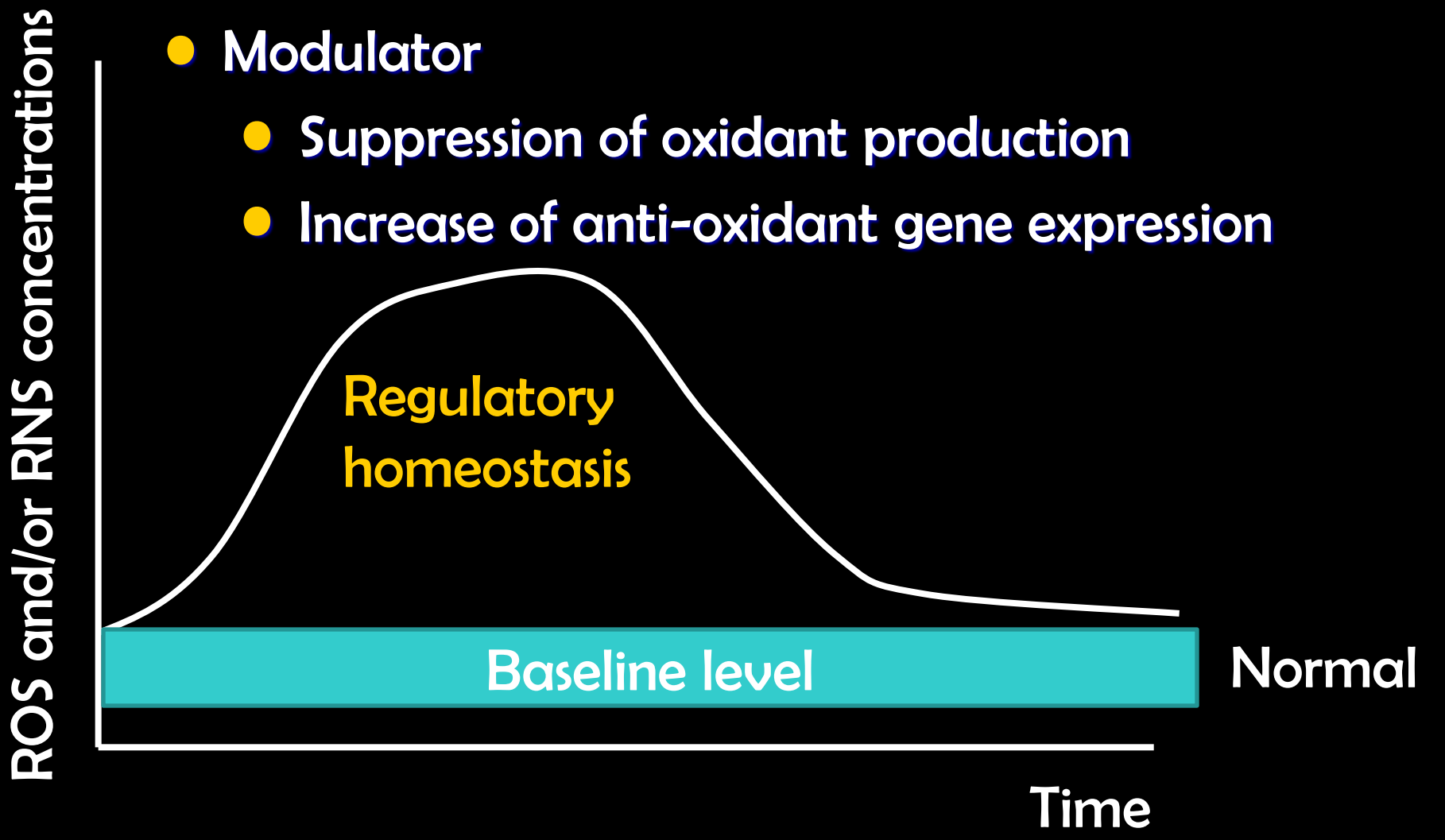


ROS activates multiple pathways



Finkel & Holbrook, Nature (2000)

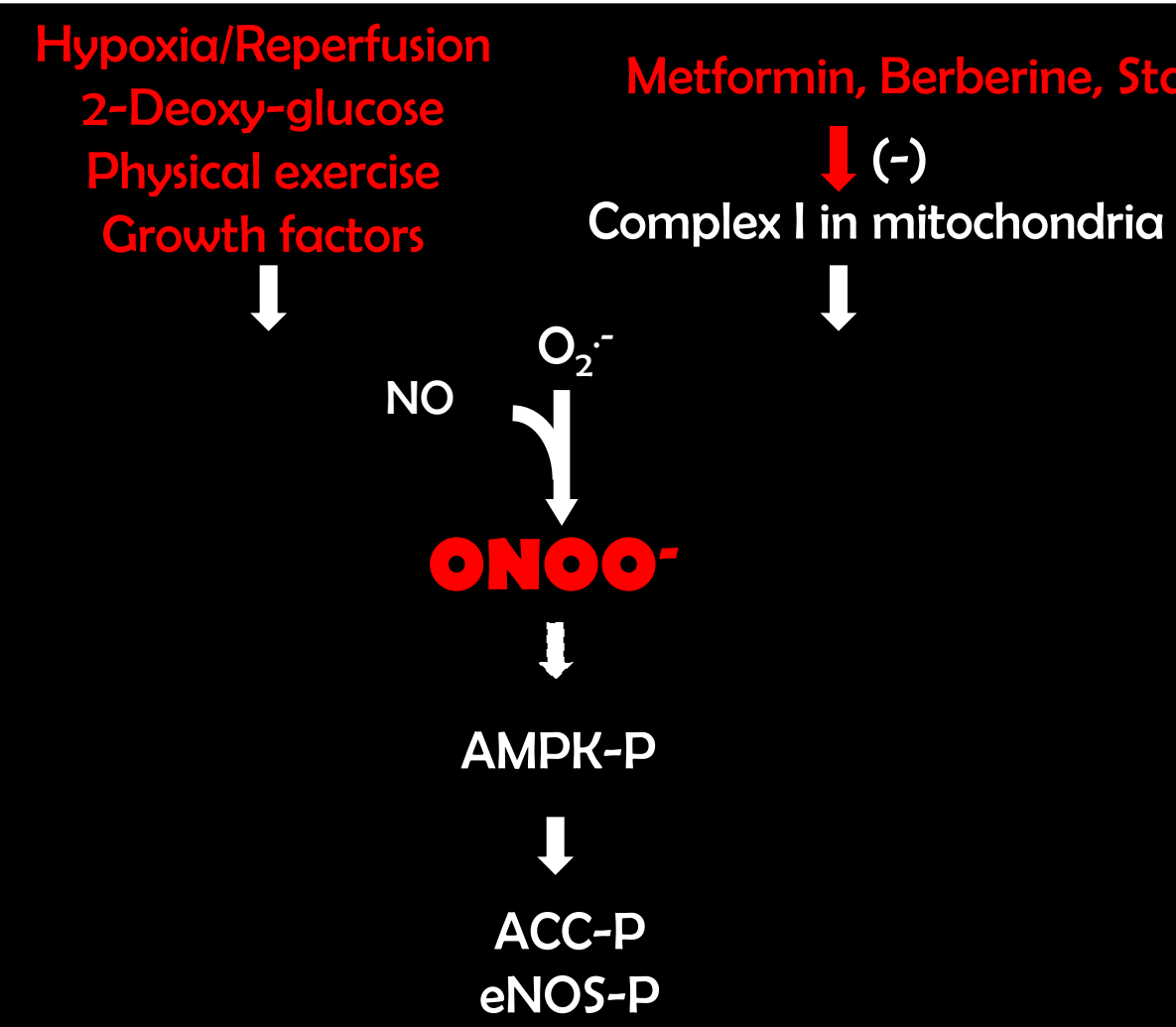
- Sensor
- Modulator
  - Suppression of oxidant production
  - Increase of anti-oxidant gene expression



How does the endothelial cell sense and modulate oxidative stress?

AMPK as A Redox Sensor and Modulator

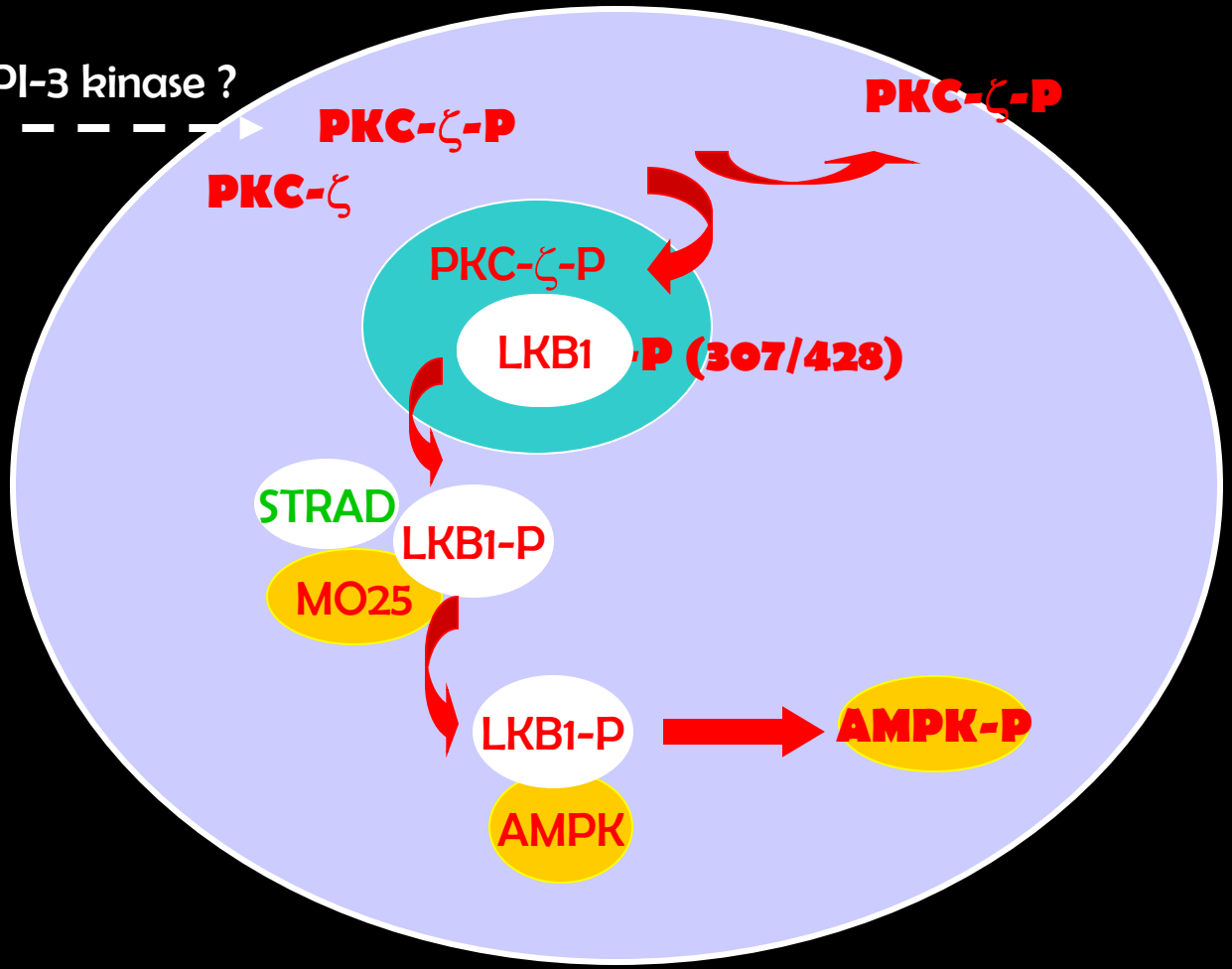
$ONOO^-$ -dependent AMPK activation in Endothelial Cells



Zou, et al., JBC 2002; Zou, et al., JBC 2003, Zou, et al 2004, Choi, et al., 2008; Xie, et al., Diabetes, 2009, Wang, S., Circ Res., et al., Wang, S., et al, PLoS One, 2011

Proposed mechanism for oxidant-dependent AMPK activation ($ONOO^-$ as a signaling)

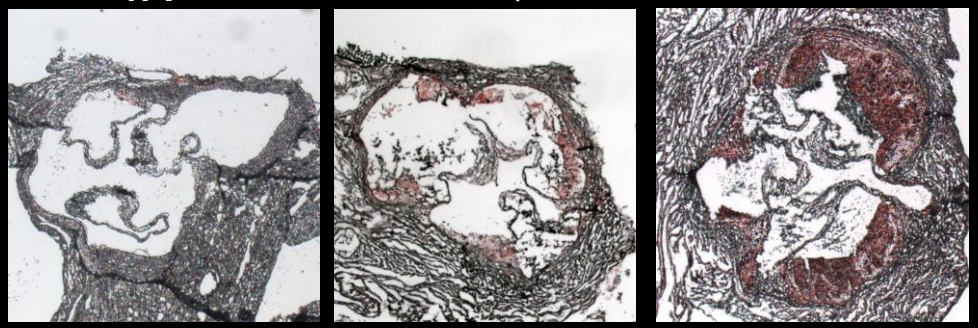
Exercise, CR /Metformin, Statin



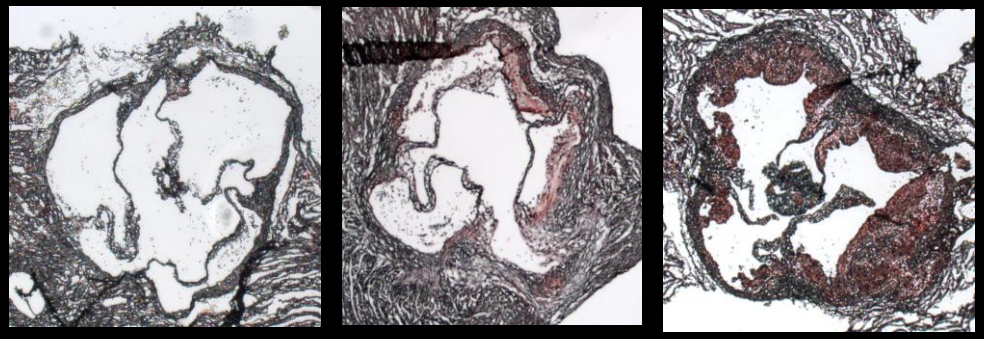
AMPK as a redox modulator:

AMPK depletion accentuates oxidant stress, endothelial dysfunction, and atherosclerosis in vivo

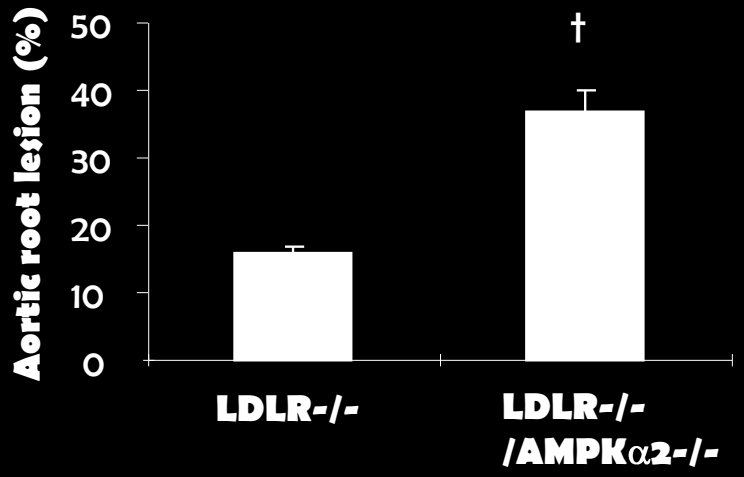
AMPK depletion and Atherosclerosis in LDLr KO mice

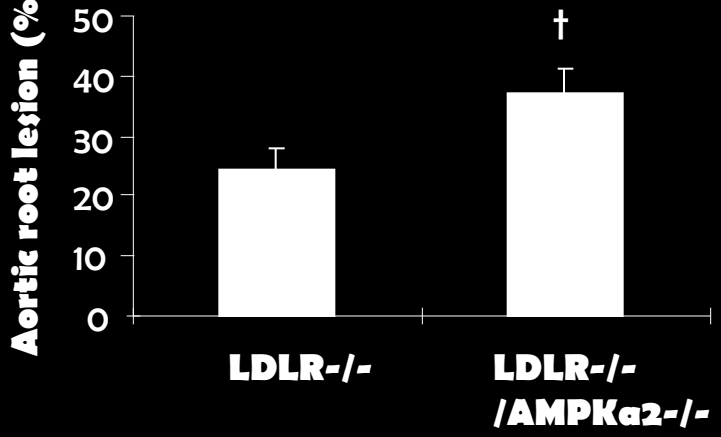


Female



Male





Wang, et al., Circ. Res. 106:1117-1128, 2010

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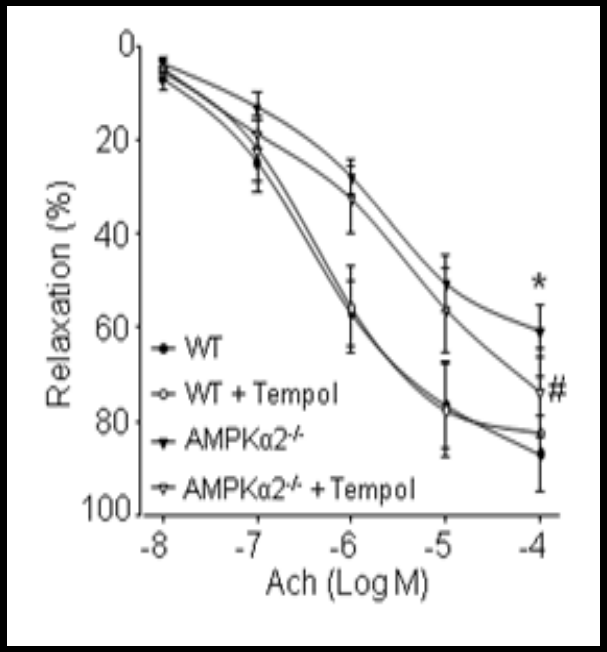
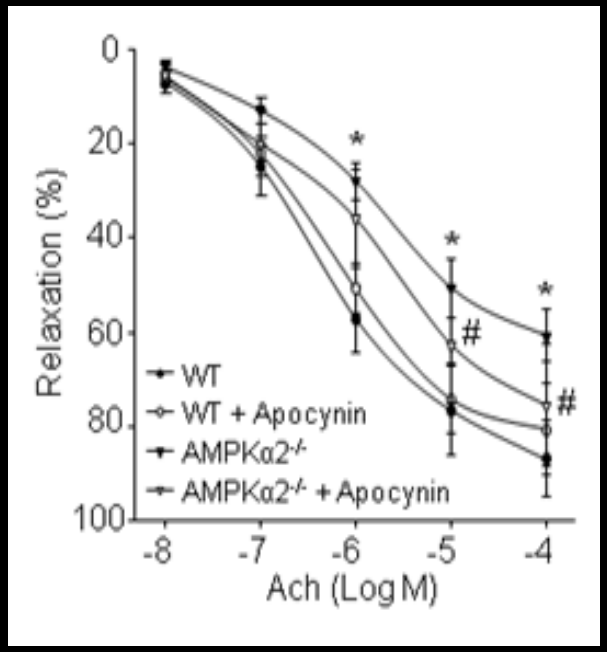
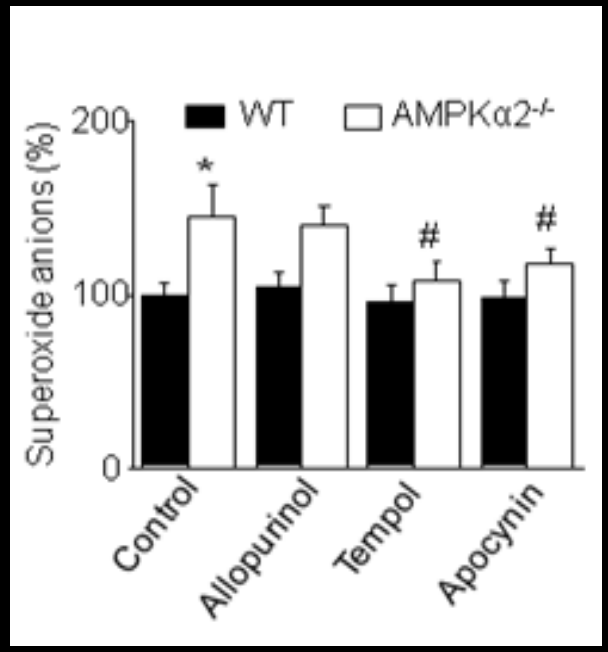
AMPK-α2 deletion increases NADPH-oxidase-dependent Superoxide and impairs endothelial function

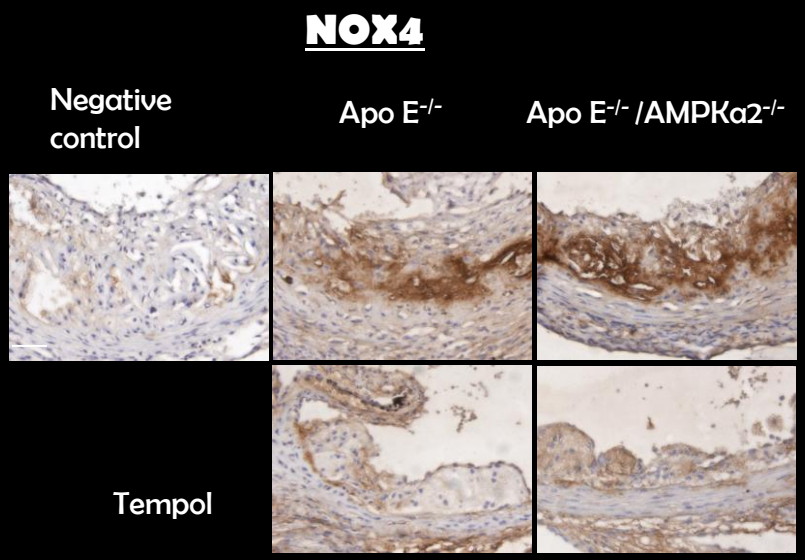


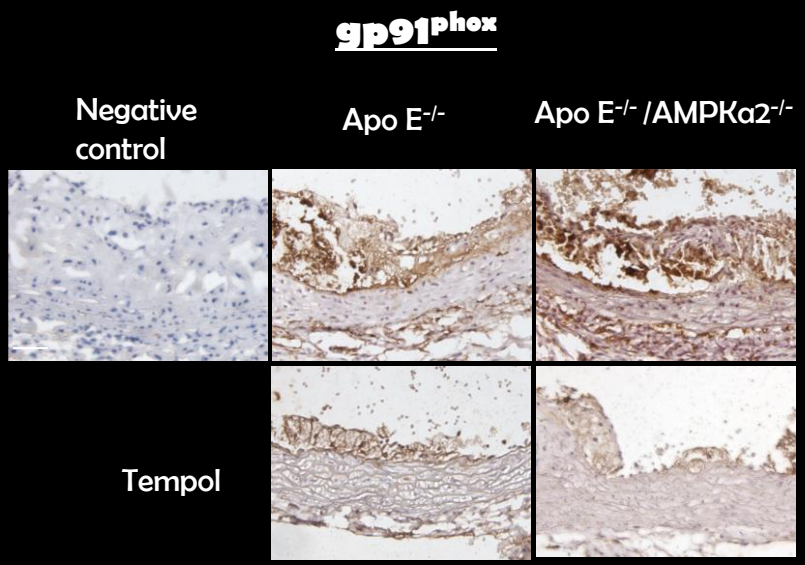


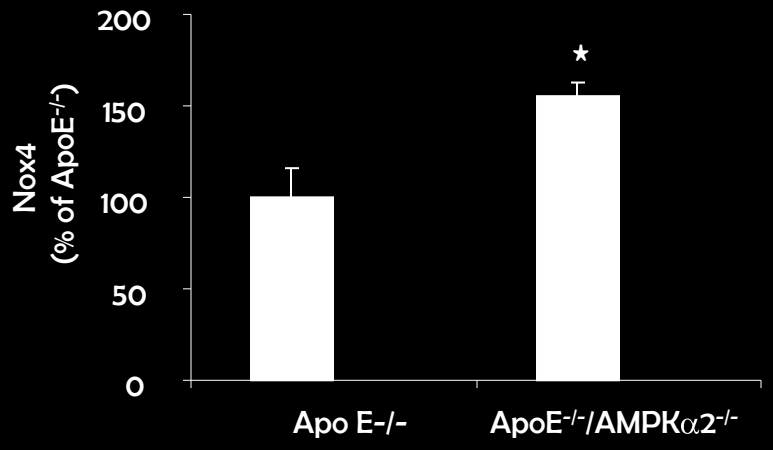


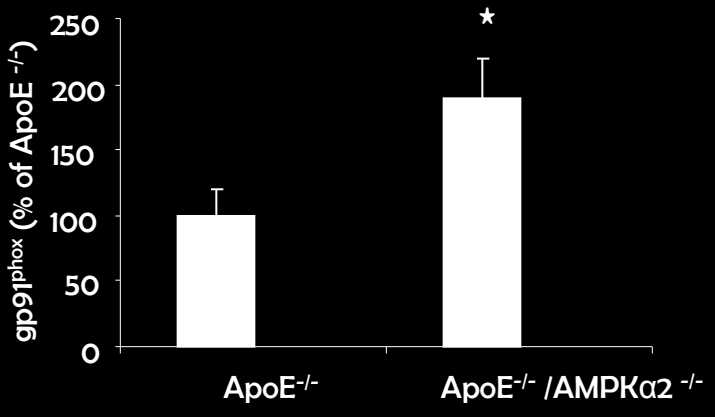
Wang, et al., Circ. Res., 2010

Increased expression of NOX-4 and NOX-2 (gp91^{phox}) in ApoE/AMPK dual KO mice









Wang, et al., Circ. Res. 106:1117-1128, 2010

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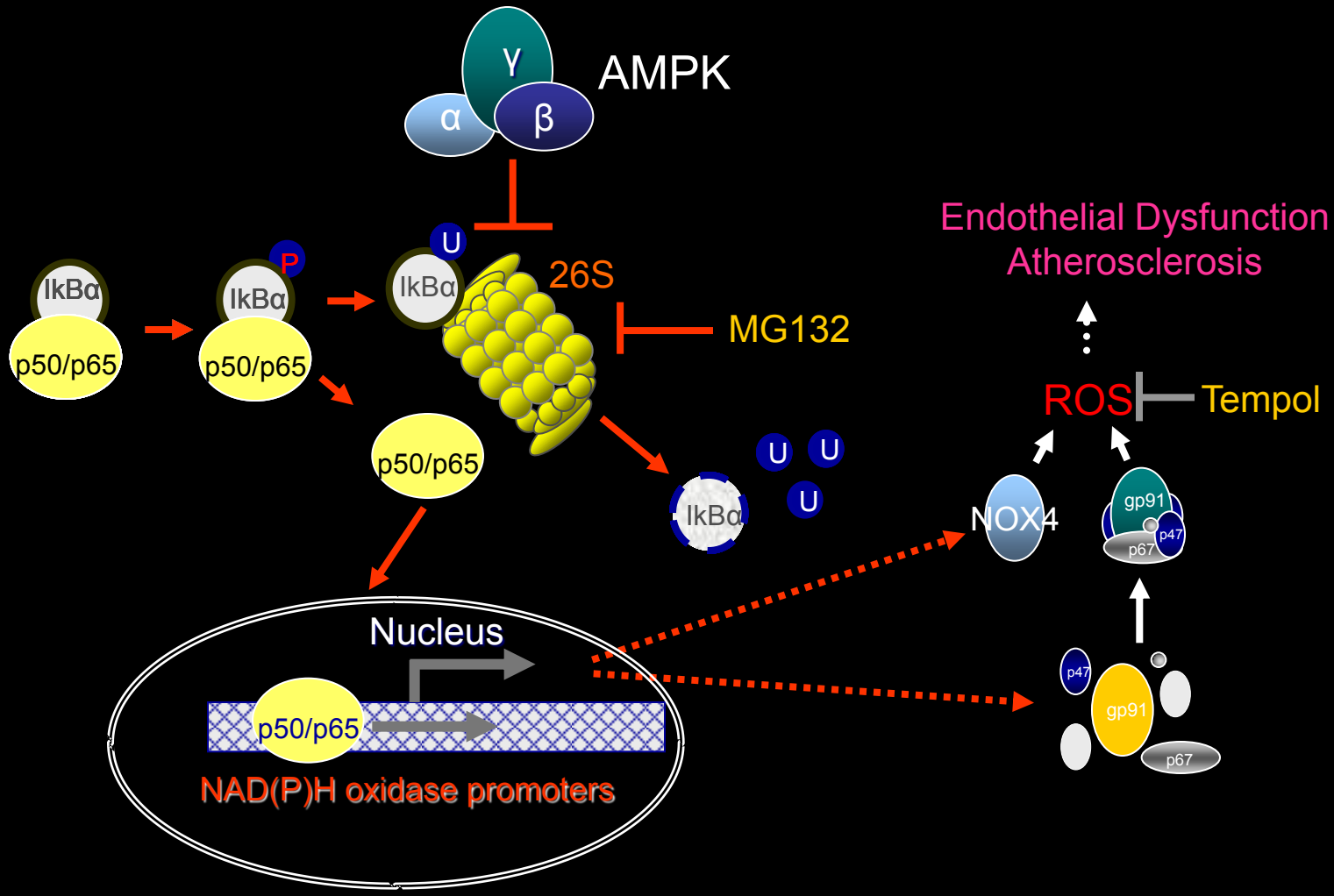
Proposed mechanism for a AMPK-dependent, 26S proteasome -dependent NAD(P)H oxidase inhibition in endothelial cells



Wang, et al., Circ. Res. 106:1117-1128, 2010

Reduction of AMP-Activated Protein Kinase α2 Increases Endoplasmic Reticulum Stress and Atherosclerosis In Vivo

Yunzhou Dong, PhD*; Miao Zhang, MD, PhD*; Bin Liang, MD, PhD; Zhonglin Xie, MD, PhD; Zhengxing Zhao, MSc; Sima Asfa, MSc; Hyoung Chul Choi, MD, PhD; Ming-Hui Zou, MD, PhD

Dong, et al., Circulation 121:792-803, 2010

AMPK inhibition → ROS → SERCA oxidation → Intracellular Ca^{2+} → ER Stress

ER Stress → Endothelial dysfunction → Atherosclerosis

Acknowledgement

Collaborators

Albert Einstein College of Medicine
Dr. Michal Brownlee

University of Washington
Dr. Rong Tian

University of Paris V
Dr. Benoit Viollet

University of Massachusetts
Dr. John F. Keaney Jr.

Funding

National Heart, Lung, Blood Institutes
Established Investigator Award of American Heart Association (AHA)
American Diabetes Association (ADA)
Juvenile Diabetes Foundation (JDRF)
Oklahoma Center for Advanced Science and Technology (OCAST)

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