Mitochondrial Biogenesis and Redox Regulation

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Mitochondrial Biogenesis and Redox Regulation

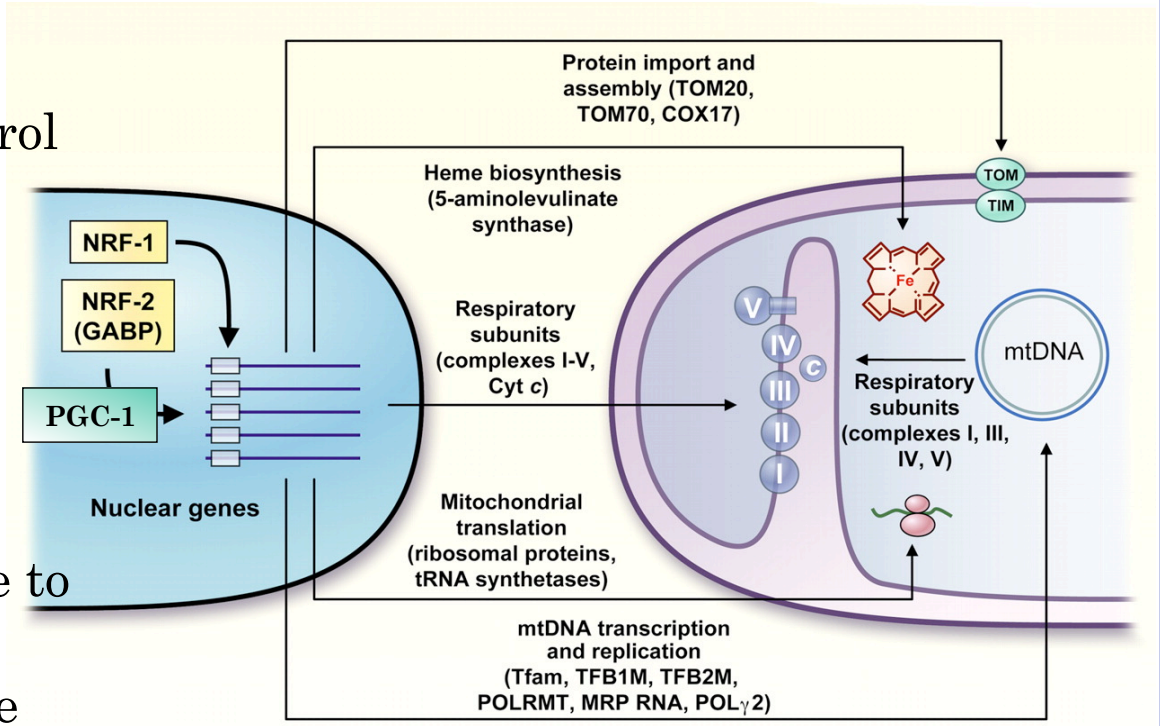
- Objectives
  - Provide an overview of the physiological and pathological states and transcriptional control mechanisms involved in mitochondrial biogenesis
  - Define how specific adjustments in cellular and/or mitochondrial redox state activate mitochondrial biogenesis
  - Illustrate the role of redox-regulation of mitochondrial biogenesis in the resolution of mitochondrial damage during acute inflammation

Mitochondrial Biogenesis and Redox Regulation

- List of Abbreviations
  - AMPK: AMP-activated kinase
  - CREB: Cyclic AMP-responsive element-binding protein 1
  - ERRa: Estrogen-related receptor alpha
  - Keap1: Kelch-like ECH-associated protein 1
  - NAMPT: nicotinamide phosphoribosyltransferase
  - Nfe2l2: Nuclear factor erythroid 2-related factor 2 (Nrf2)
  - NRF-1/NRF-2: Nuclear respiratory factors-1 and -2 (GABP)
  - PGAM5: Mitochondrial serine/threonine phosphatase
  - PGC-1a: Peroxisome proliferator-activated receptor gamma co-activator 1-alpha
  - PPARa: Peroxisome proliferator-activated receptor alpha
  - RIP140: Nuclear receptor-interacting protein 1
  - SIRT1: NAD-dependent deacetylase sirtuin-1

Mitochondrial Biogenesis and Redox Regulation

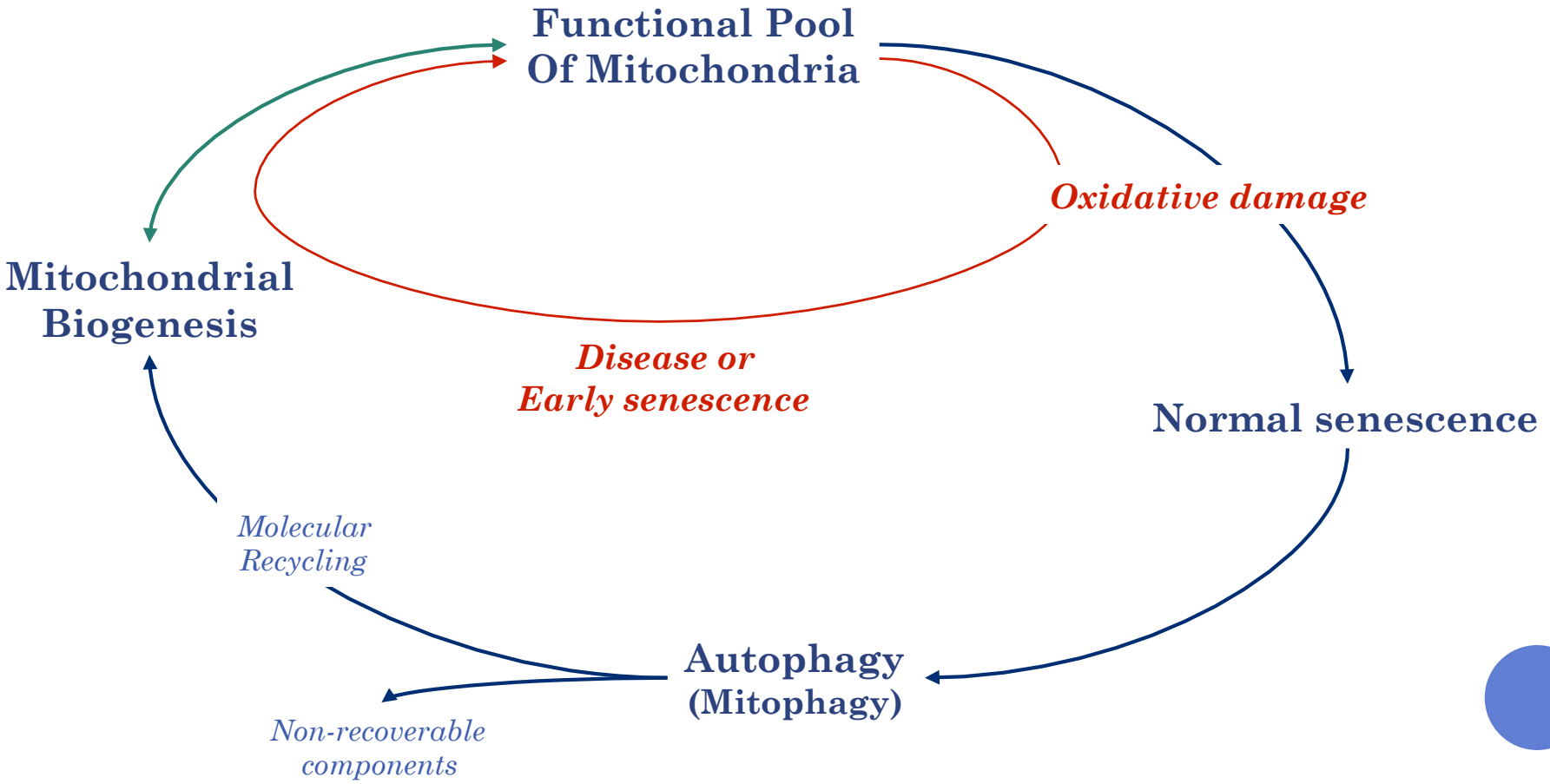
- Bi-genomic transcriptional network integral to mitochondrial quality control
- Coordinated with energy needs, cell growth, proliferation, autophagy
- Homeostatic, adaptive, anti-oxidant, anti-inflammatory
- Part of integrated response to tissue damage and disease
- Major control pathways are under redox-regulation



Scarpulla,R. *Physiol Rev* 2008;88:611-638

Mitochondrial Biogenesis and Redox Regulation

- Mitochondrial Quality Control (no *de novo* synthesis)



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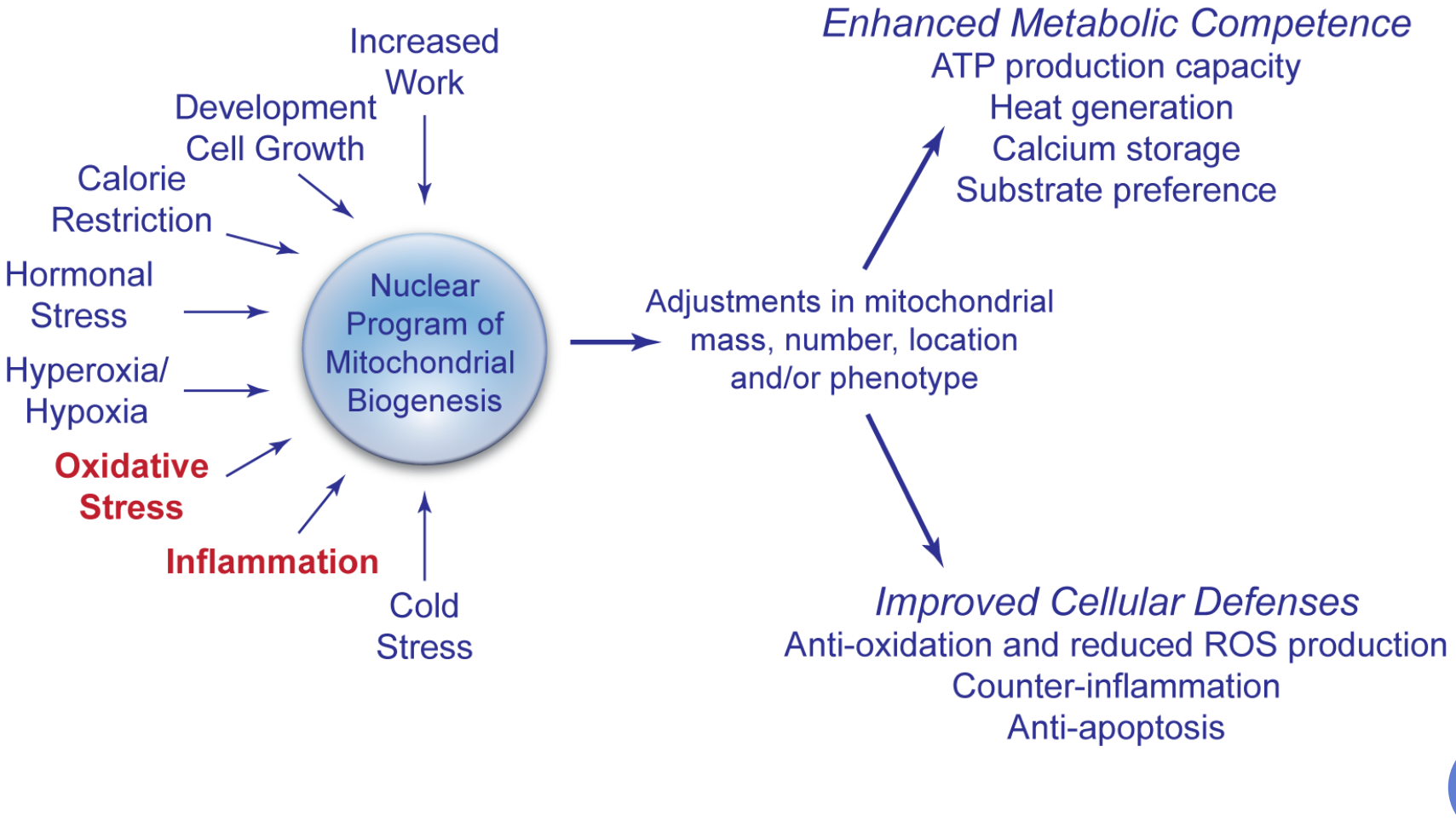

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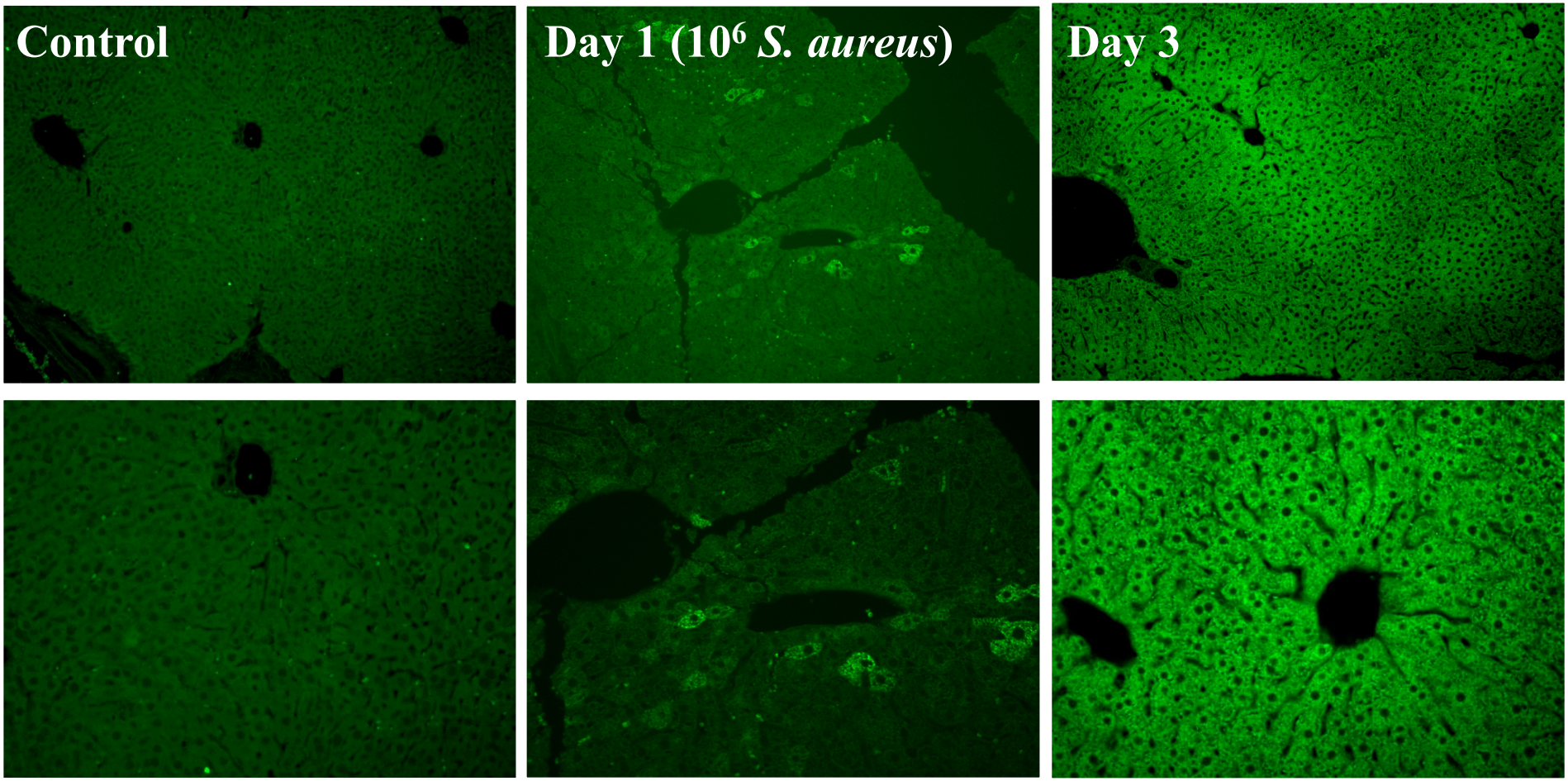
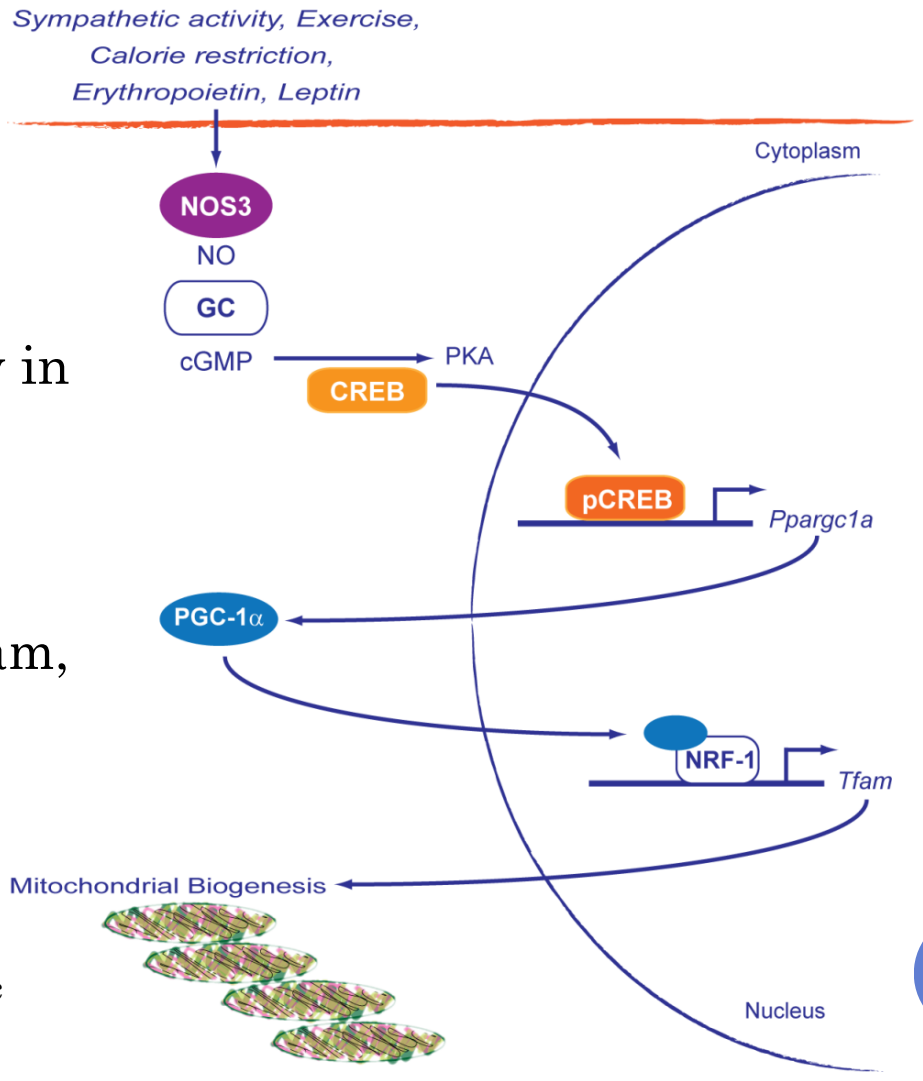


Mitochondrial Biogenesis and Redox Regulation

- Major types of induction mechanisms for nuclear-encoded mitochondrial genes
  - Energy-sensing pathways
  - AMPK
  - **SIRT1**
  - **CREB**
- Ca^{++}-dependent kinases
  - CaMK II/IV, CaMKK
  - Calcineurin A
  - **p38g MAPK**
- Redox-regulated pathways
  - **NO/cGMP**
  - **Nrf2/HO-1/CO**
- Inflammatory pathways
  - **NF-kB**
  - **CREB**

Mitochondrial Biogenesis and Redox Regulation

- NO and mitochondrial biogenesis
  - cGMP production by multiple factors either directly or through an increase in eNOS activity in muscle, fat, other tissues up-regulates regulatory genes for mitochondrial biogenesis including PGC-1α, NRF-1, and Tfam, leading to mitochondrial proliferation



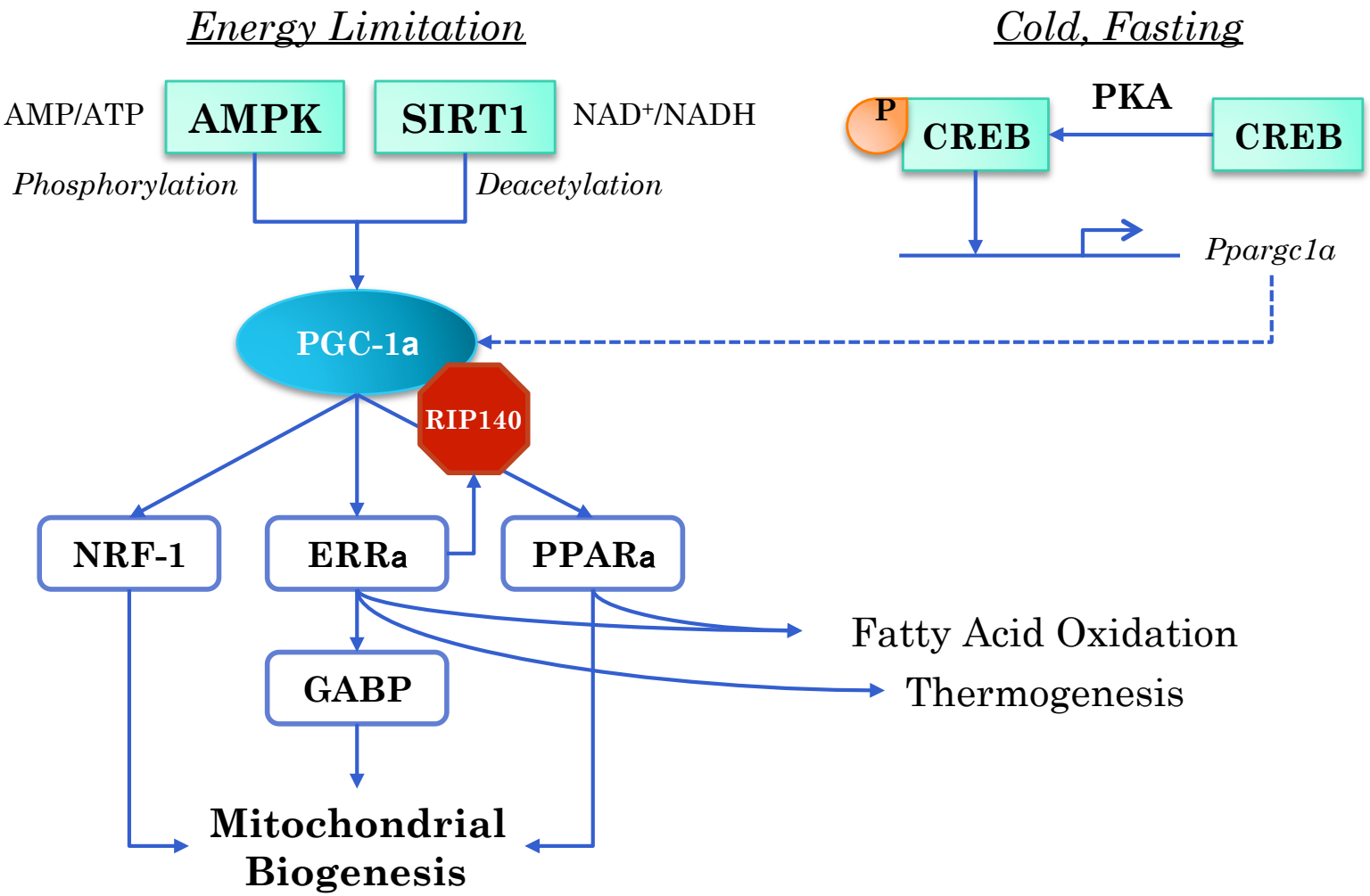
Modified from Nisoli E, Carruba MO. Nitric oxide and mitochondrial biogenesis. *J Cell Sci*. 2006;119:2855–2862.

Mitochondrial Biogenesis and Redox Regulation

- PGC-1 co-activator family members act as coordinators of mitochondrial biogenesis
  - PGC-1a
  - PGC-1b
  - PRC
- Partner with DNA binding transcription factors (e.g. NRF-1, GABP and CREB) to activate 500-1,000 nuclear-encoded mitochondrial genes needed for mitochondrial proliferation

Vercauteren K., Pasko R.A., Gleyzer N., Marino V.M., Scarpulla R.C. PGC-1-related coactivator: immediate early expression and characterization of a CREB/NRF-1 binding domain associated with cytochrome c promoter occupancy and respiratory growth. *Mol. Cell. Biol.* 26:7409-7419, 2006

Mitochondrial Biogenesis and Redox Regulation



Mitochondrial Biogenesis and Redox Regulation

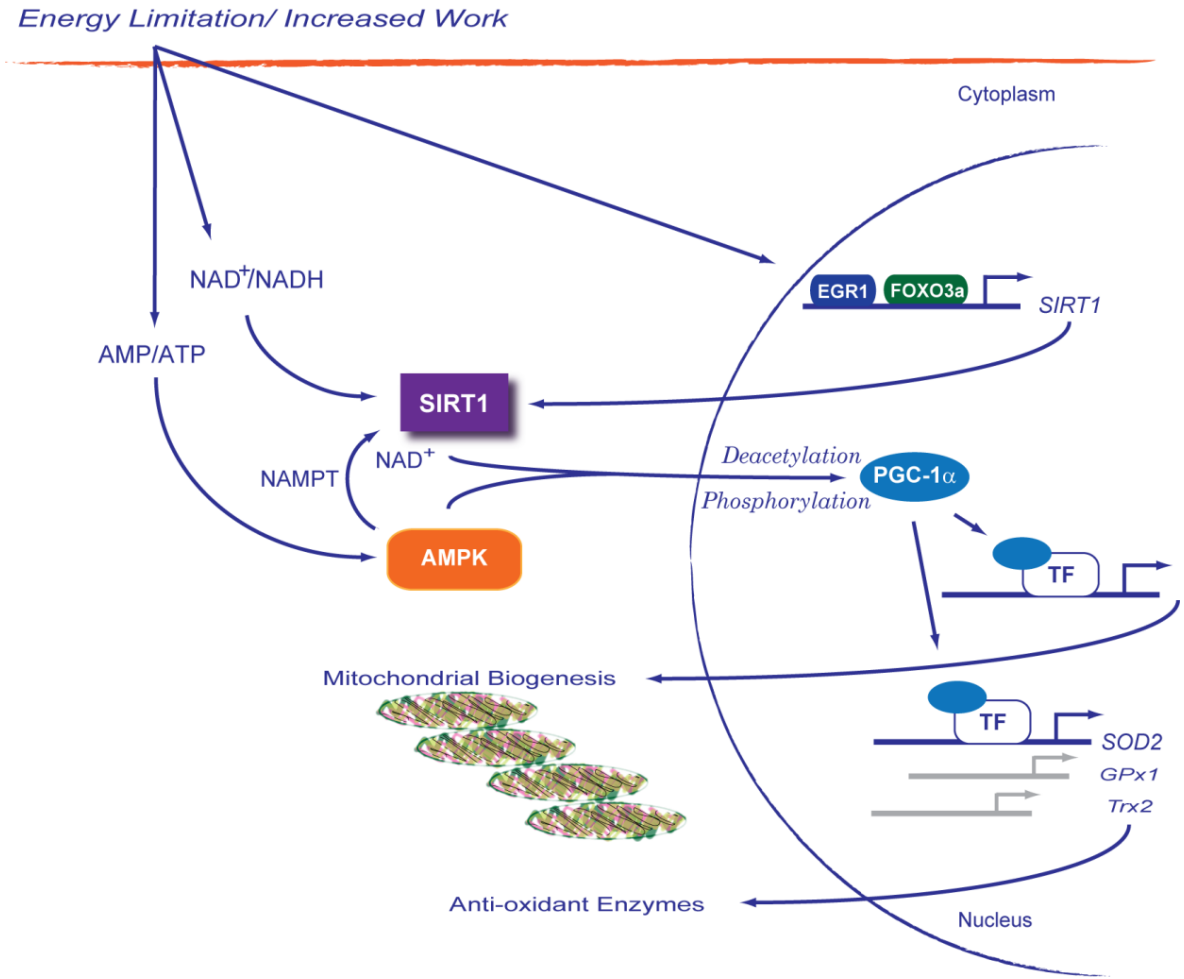
- SIRT1
  - NAD^+-dependent histone deacetylase (class III HDAC)
  - Deacetylates diverse histone and non-histone proteins
  - Mediates effect of calorie restriction on lifespan and cell metabolism
  - Anti-inflammatory effect through down-regulation of NF-kB-dependent pro-inflammatory cytokine expression

Mitochondrial Biogenesis and Redox Regulation

- AMPK
  - Senses metabolic stress and energy deprivation (AMP/ATP); activated by muscle contraction (Ca^{2+}/ROS)
  - Stimulates fatty acid breakdown, glycolysis
  - Inhibits energy-utilizing synthetic pathways (protein, cholesterol, fatty acids)
  - Activates PGC-1α by phosphorylating Thr^{177} and Ser^{538}
  - Activates SIRT1 by increasing NAD^+/NADH through β-oxidation and stimulation of nicotinamide phosphoribosyltransferase (NAMPT), the rate-limiting step in NAD biosynthesis

Mitochondrial Biogenesis and Redox Regulation

- SIRT1 and AMPK cooperate to activate PGC-1a



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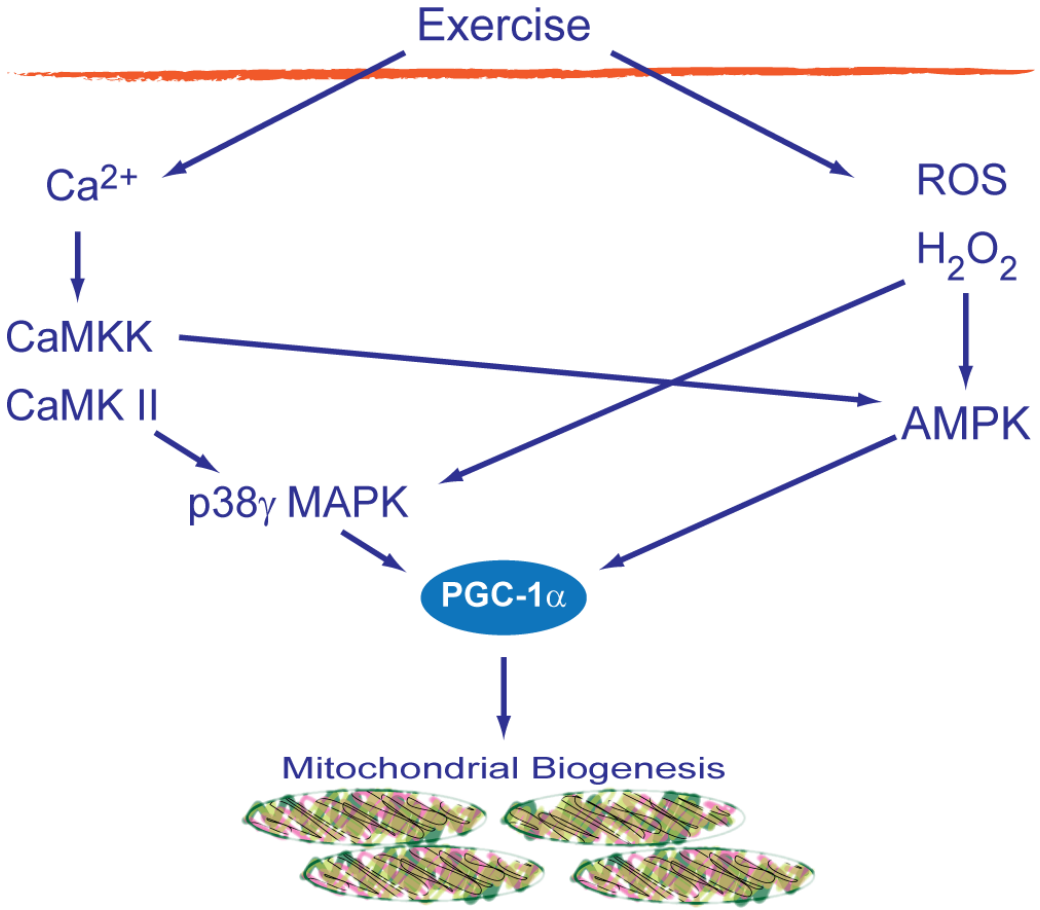
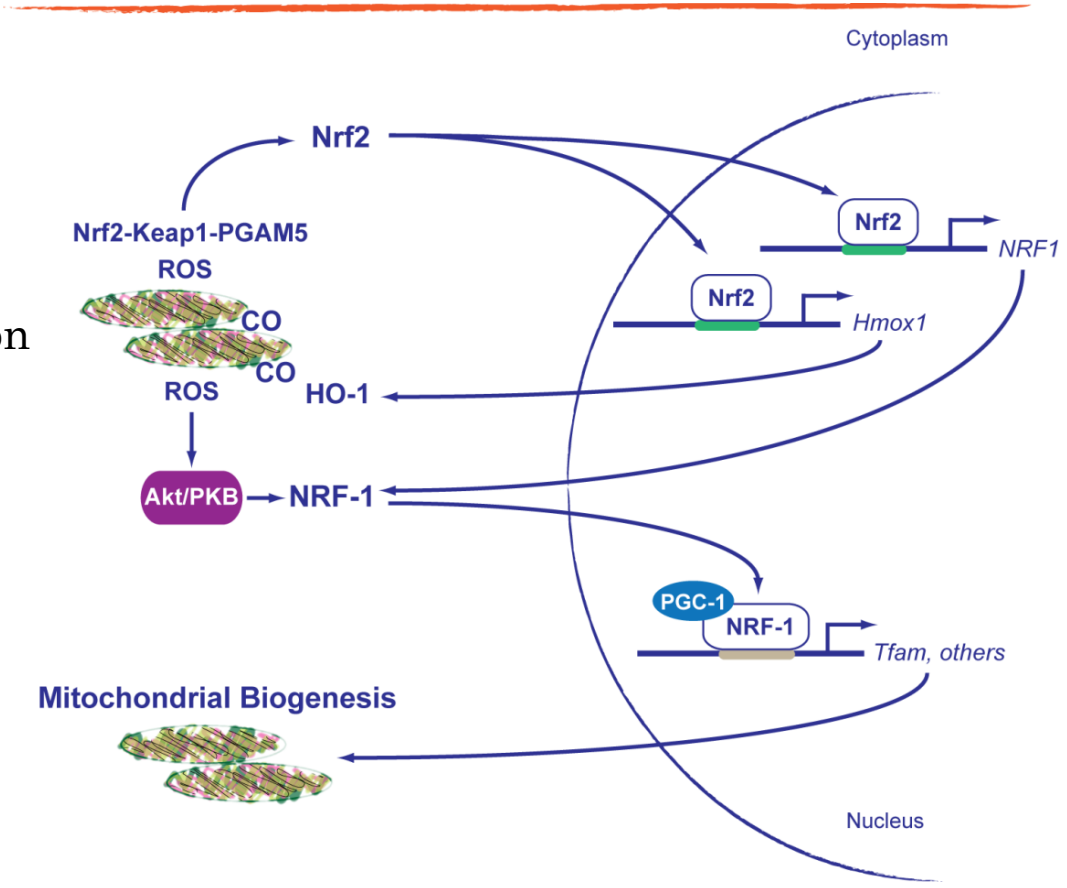
- Ca^{2+} vs. ROS in exercise-induced mitochondrial biogenesis



Modified from Lira V A *et al. Am J Physiol Endocrinol Metab* 299:E145-E161, 2010

Mitochondrial Biogenesis and Redox Regulation

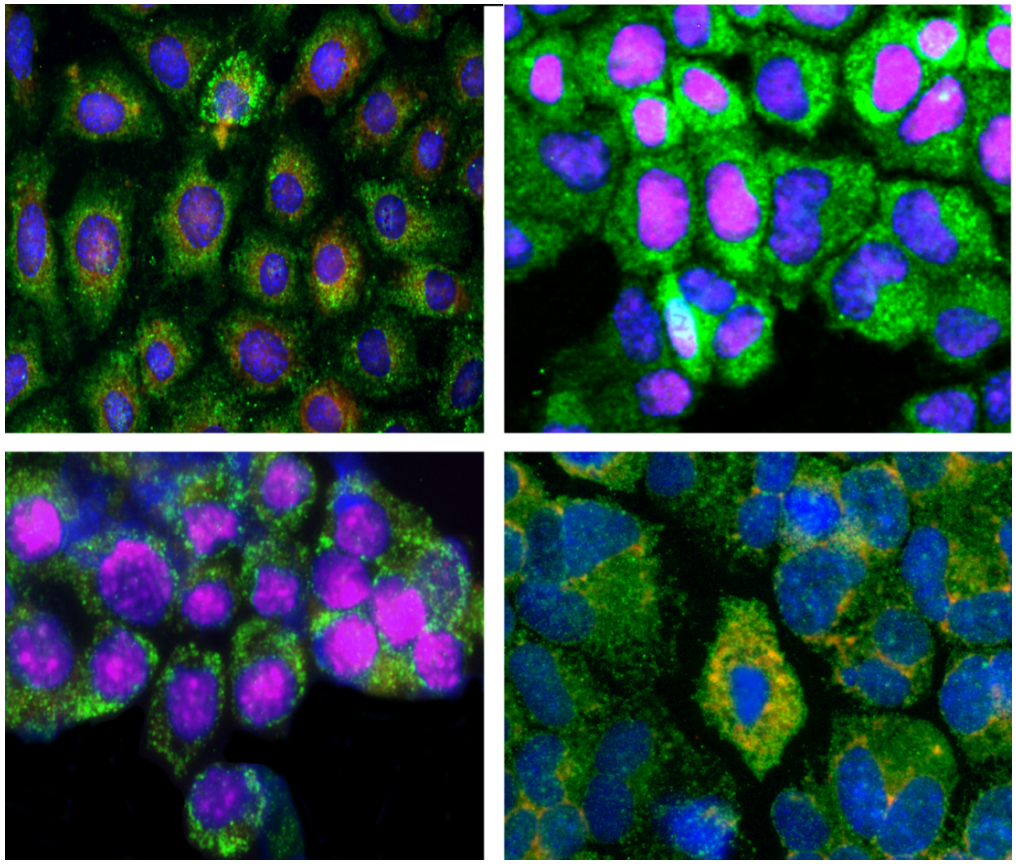
- Heme oxygenase-1 (HO-1; *Hmox1*)
  - Inducible heme catabolism
    - Breaks a-methene carbon bond releasing Fe, CO, biliverdin
  - Potent anti-inflammatory, pro-survival effects
  - HO-1/CO induces mitochondrial biogenesis



Suliman HB, *et al*. A new activating role for CO in cardiac mitochondrial biogenesis. *J Cell Sci*. 120:299-308, 2007

Mitochondrial Biogenesis and Redox Regulation

- HO-1/CO induction of mitochondrial biogenesis



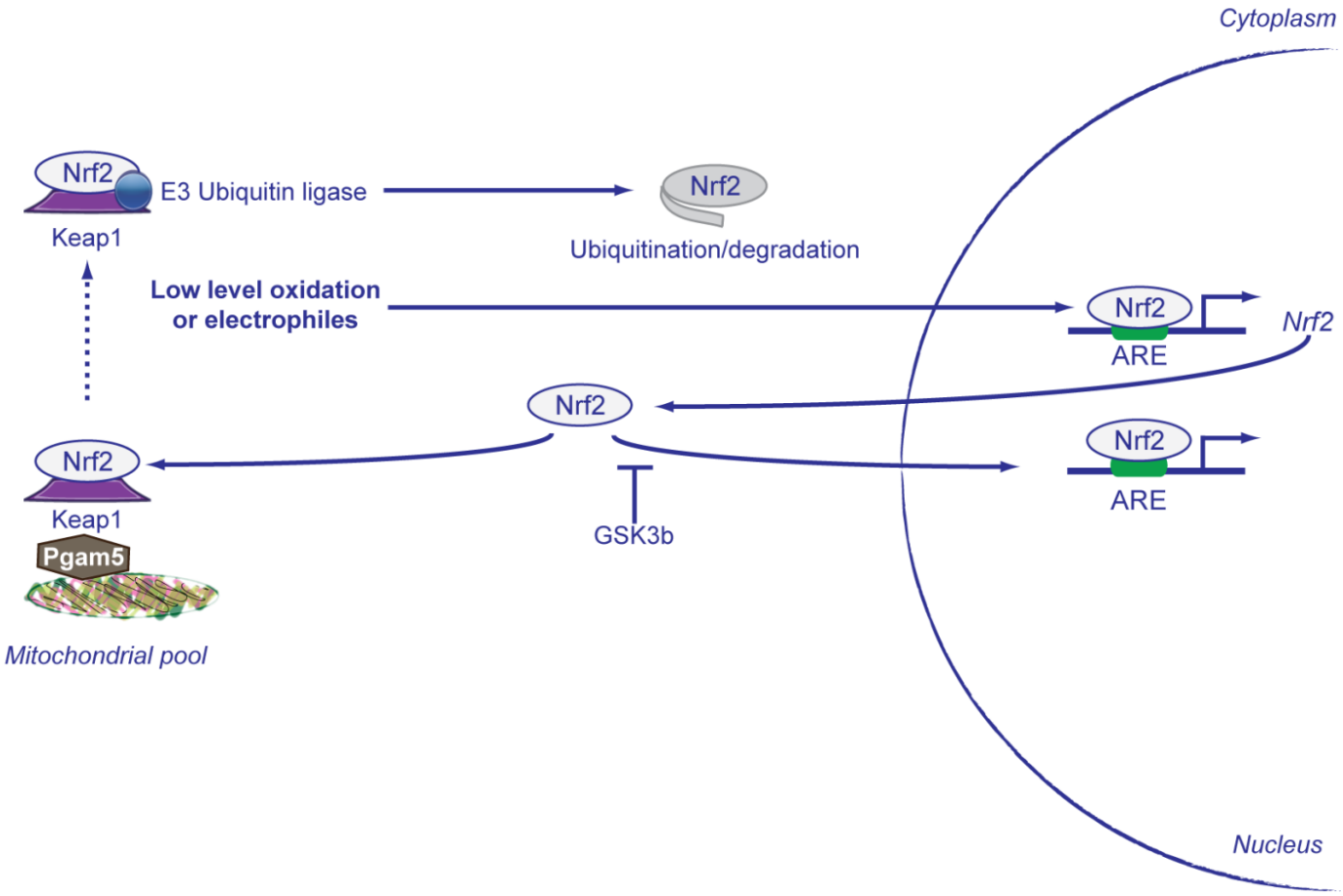
Green, Mitotracker; Red, NRF-1; Blue, Dapi

Mitochondrial Biogenesis and Redox Regulation

- Key role of Nrf2 (Nfe2l2)
  - Basic leucine-zipper "CNC" transcription factor that binds to antioxidant response elements (ARE) in promoter regions of target genes, e.g. *Nqo1*, *GST*, *Hmox1*
  - Forms ternary docking complex with Pgam5 (outer mitochondrial membrane) and Keap1 (cytoplasmic inhibitor)
    - Keap1 cysteine oxidation stabilizes complex and prevents degradation
    - Nrf2 Ser^{40} phosphorylation by PKC dissociates Nrf2 from Keap1 in response to oxidative stress
  - Widely expressed in kidney, muscle, lung, heart, liver, brain

Mitochondrial Biogenesis and Redox Regulation

- Normal cytoplasmic turnover of Nrf2



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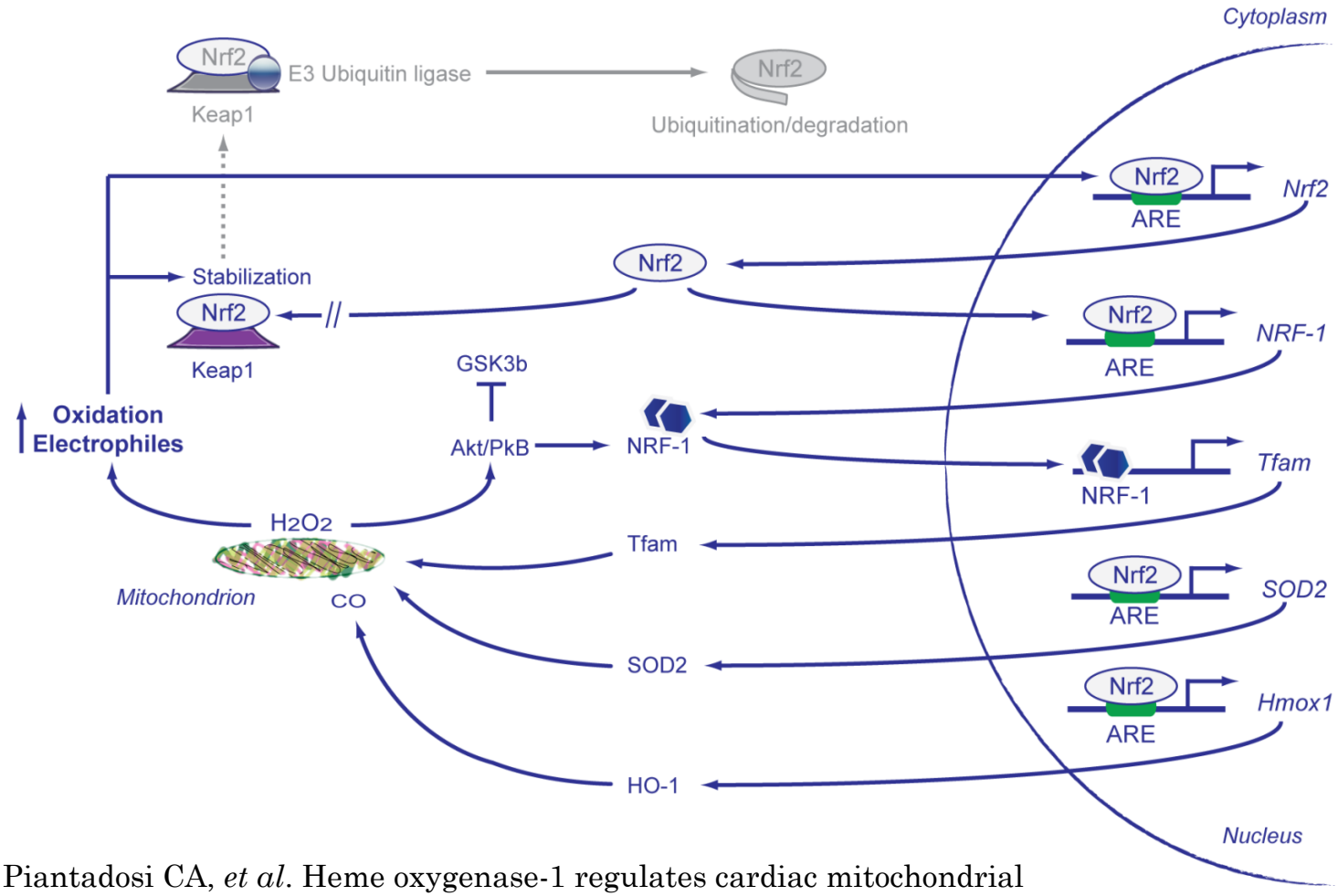

Piantadosi CA, *et al*. Heme oxygenase-1 regulates cardiac mitochondrial biogenesis via Nrf2-mediated transcriptional control of nuclear respiratory factor-1. *Circ Res*. 103(11):1232-40, 2008

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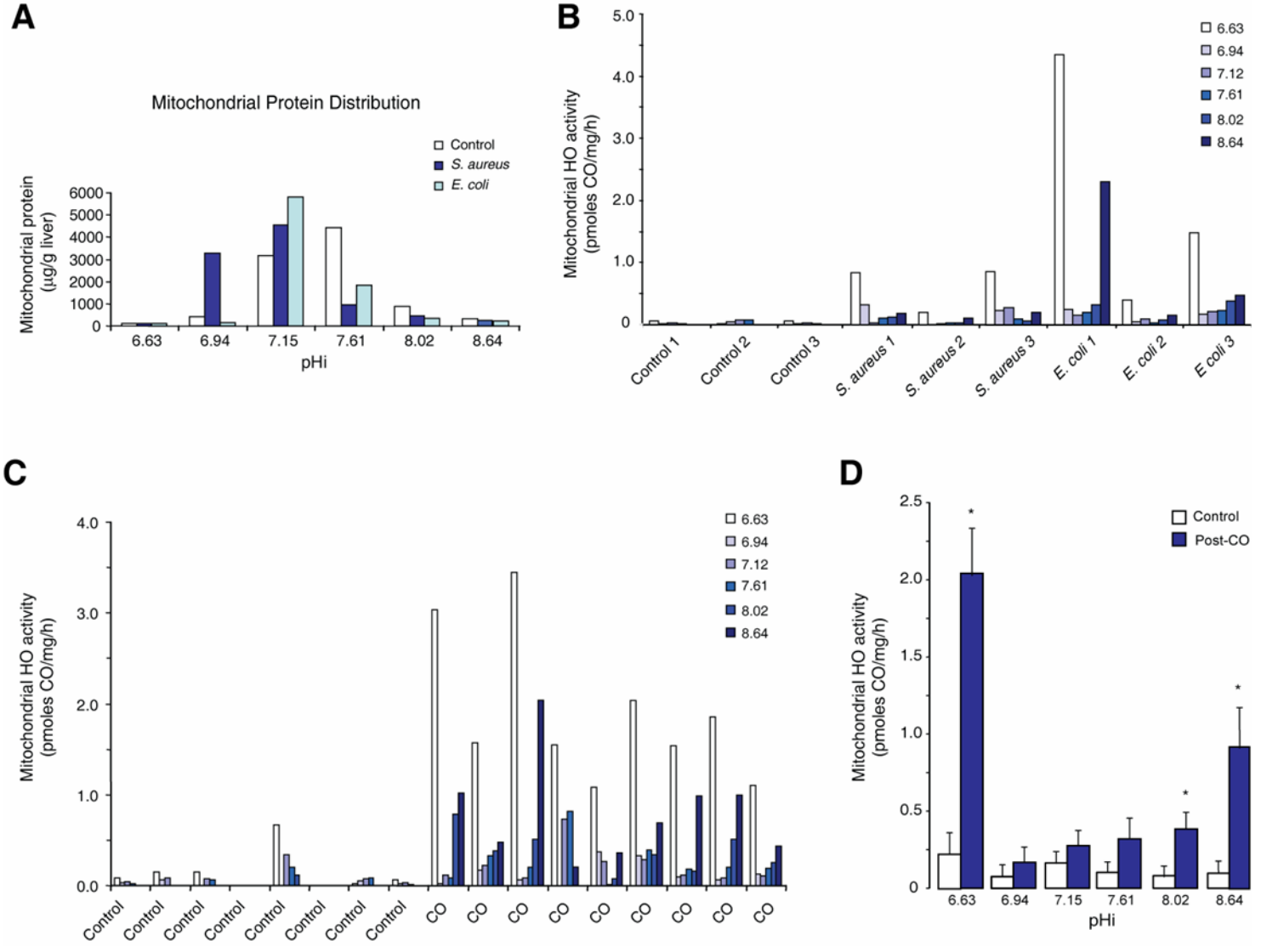

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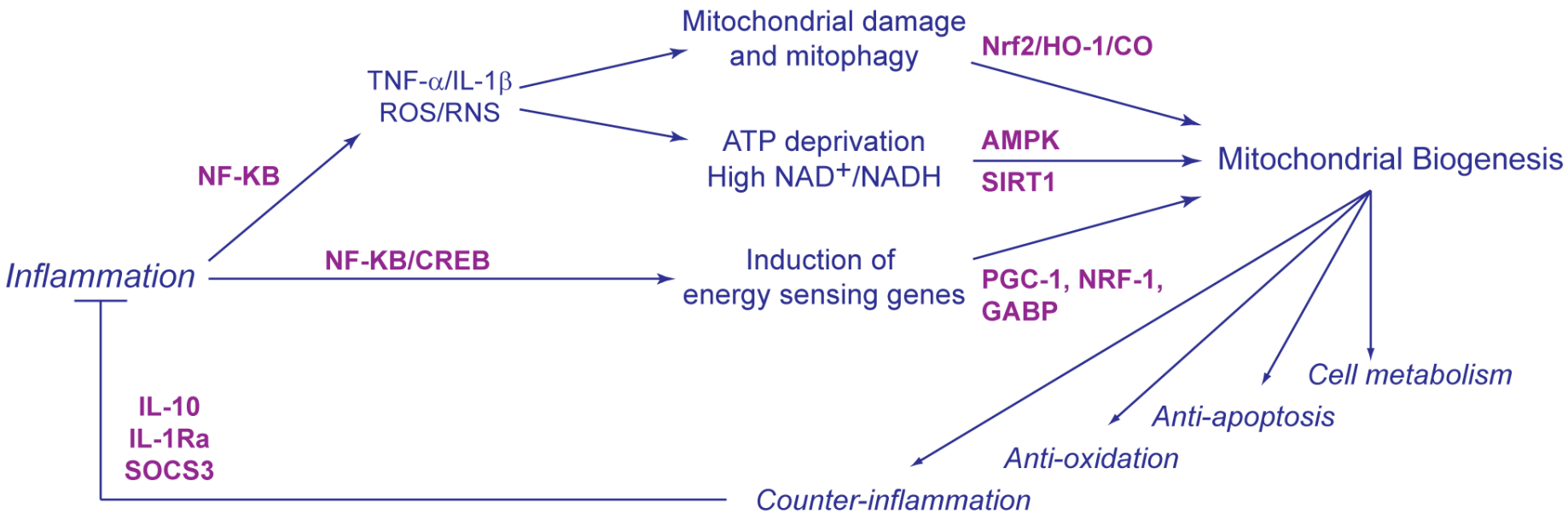
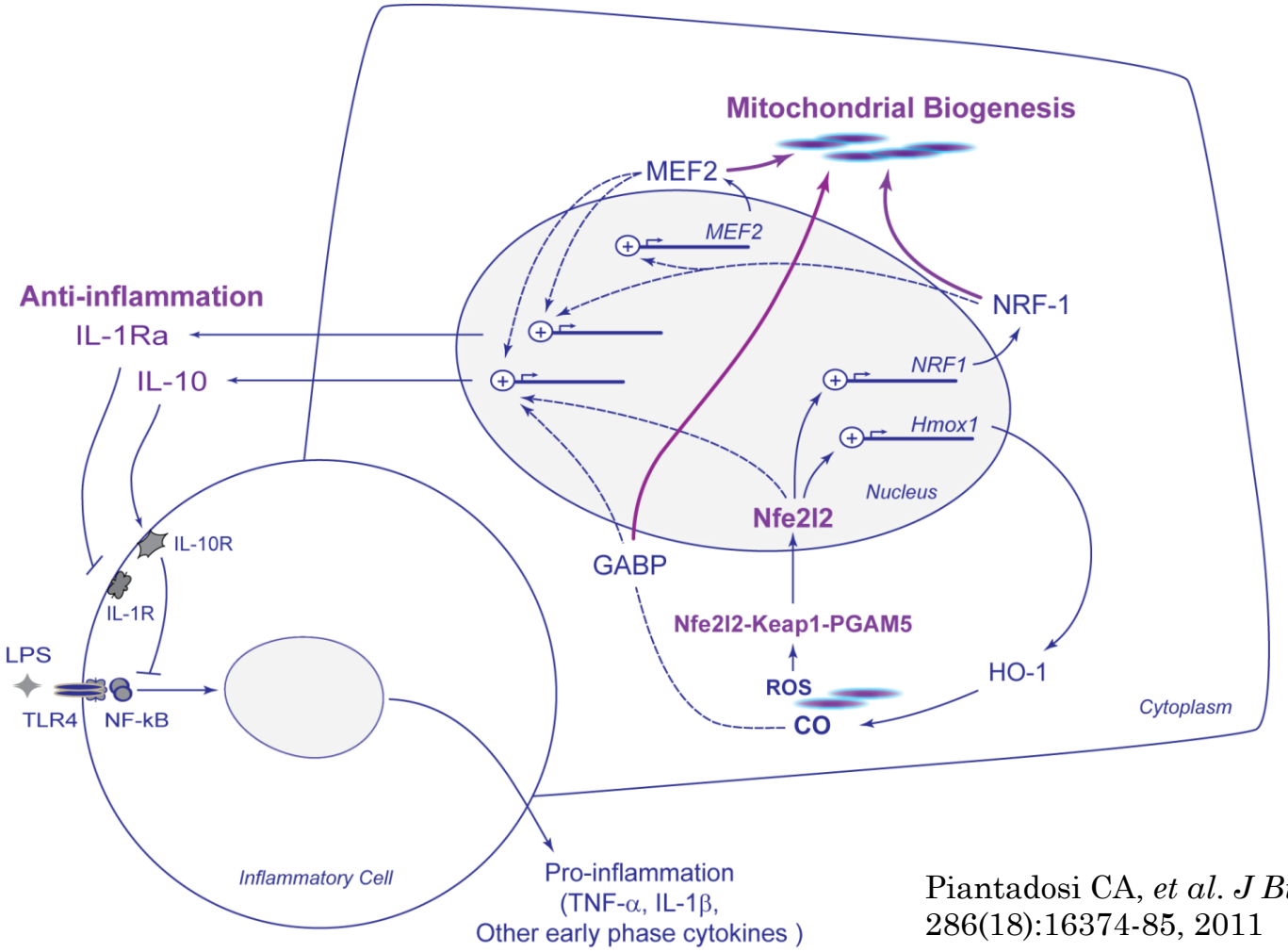
- Effects of inflammation on mitochondrial quality control



Mitochondrial Biogenesis and Redox Regulation

- Counter-inflammation



Piantadosi CA, *et al. J Biol Chem.* 286(18):16374-85, 2011

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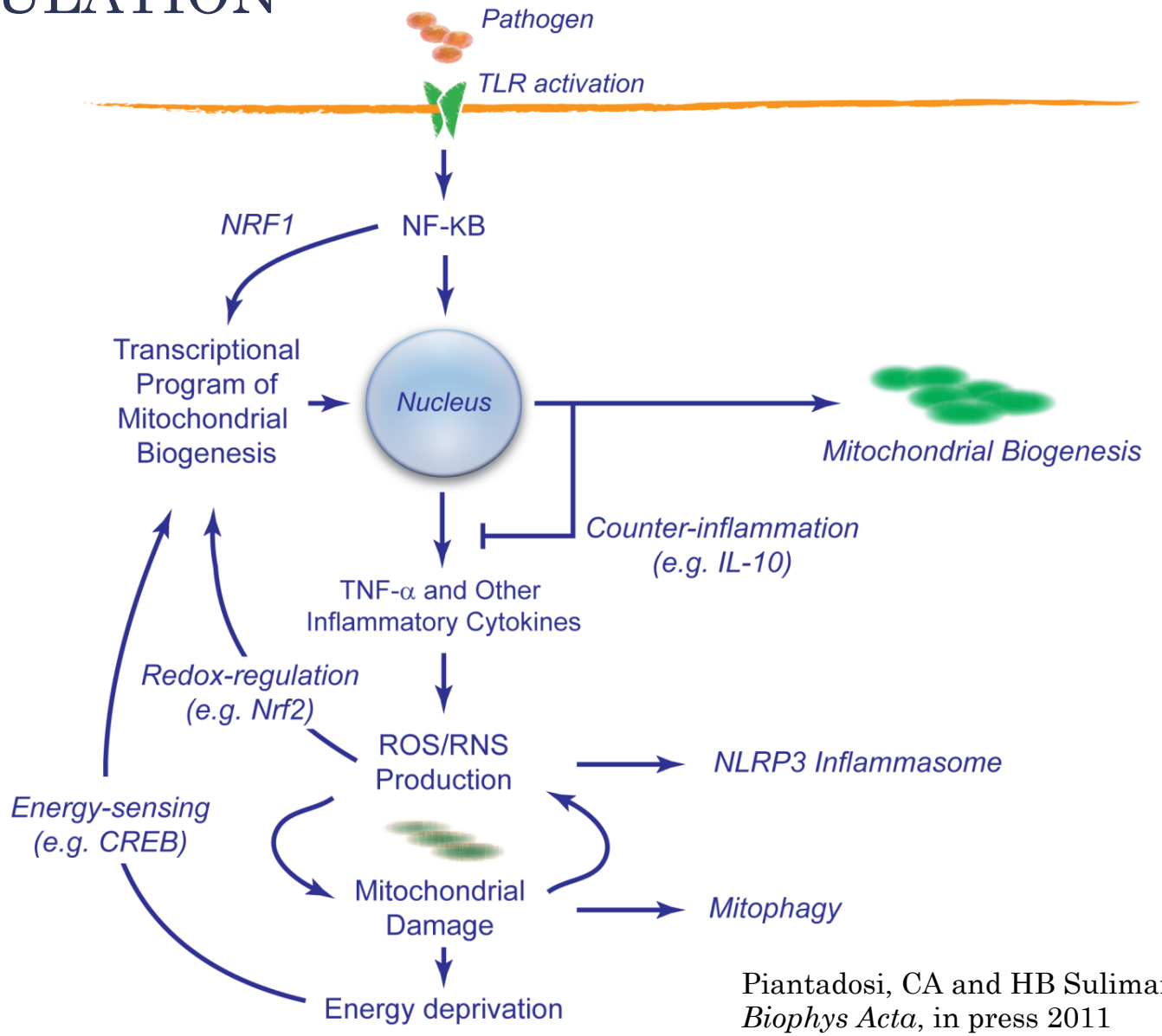

Piantadosi, CA and HB Suliman, *Biochem Biophys Acta*, in press 2011

Mitochondrial Biogenesis and Redox Regulation

- Summary/Conclusions
  - Redox regulation of mitochondrial biogenesis is a major mitochondrial quality control mechanism in mammalian cells
  - Multiple levels of redox control are involved
    - NO/cGMP
    - Nrf2/HO-1/CO
    - NAD^+/NADH ratio
    - Mitochondrial H_2O_2 production
  - Control points involve redox regulation of kinase activity and gene expression
  - The mitochondrial biogenesis transcriptional program is part of a master network of cellular anti-oxidant and anti-inflammatory defenses

Mitochondrial Biogenesis and Redox Regulation

- Collaborators
  - Hagir B. Suliman, D.V.M, Ph.D.
  - Karen E. Welty Wolf, M.D.
  - Raquel B. Bartz, M.D.
  - Timothy E. Sweeney, M.D., Ph.D.
  - Crystal Withers, M.D., Ph.D. student
  - Ping Fu, M.D.
- Funding
  - NHLBI
  - Veteran's Administration