The Emerging Molecular and Cellular Mechanisms of Vascular Dysfunction with Aging

Tony Donato
SLC VA GRECC Investigator
Department of Medicine
University of Utah
CVD is the Leading Cause of Death in the U.S.

A Total CVD
B Cancer
C Accidents
D Chronic Lower Respiratory Diseases
E Diabetes Mellitus
F Alzheimer’s Disease

Source: American Heart Association
Aging is a (the?) major risk factor for CVD.


Source: American Heart Association
The majority of CVD deaths are attributable to diseases of the arteries.

Percentage breakdown of deaths due to cardiovascular disease (United States: 2008)

- Coronary Heart Disease, 49.9%
- Stroke, 16.5%
- Heart Failure*, 7.0%
- High Blood Pressure, 7.5%
- Diseases of the Arteries, 3.4%
- Other, 15.6%
The Vascular Endothelium: Triggering Site for Atherosclerosis

Young Endothelial Cell

- NO
- ROS
- EDD

O₂ → SOD → H₂O₂ → CATALASE → H₂O + O₂

NO → NOS → O₂⁻ → NOX
Vascular endothelial dysfunction and risk of CVD with aging

Douglas R. Seals, Kristen L. Jablonski and Anthony J. Donato; *Clinical Science* 2011 120, 357-375
Aging and Endothelial Dependent Dilation

Brachial FMD Model

Forearm Blood Flow Model

Flow mediated dilation

Celermajer et al., *JACC* 1994

Maximal FBF response to Acetylcholine

Normotensive Males (n=36)

Taddei et al., *Hypertension* 1996
Mouse Model Young and Older B6D2F1 Mice: First Generation Cross of C57BL/6 and DBA Mouse

Lesniewski et al., J Gerontol: Biol Sci, 2009
Durrant et al. Journal of Physiology 2009
Donato et al. AJP Heart and Circ, 2009
Lesniewski et al. AJP Heart and Circ, 2011
Donato et al. Journal of Physiology 2011
In Vitro Artery Experiments
Age-related Endothelial Dysfunction in Isolated Skeletal Muscle Arteries from Rodents

Alterations Hypothesized to Contribute to the Process of Aging

- Oxidative Stress
- Inflammation
- Genomic instability
- Telomere attrition
- Epigenetic alterations
- Cellular senescence
- Mitochondrial dysfunction
- Loss of proteostasis
- Deregulated nutrient-sensing
Oxidative Stress a Mechanism Contributing to Endothelial Dysfunction with Aging
Endothelial nitrotyrosine and EDD with aging in men

Donato et al., Circ Res 100:1659-66, 2007
Aging, Oxidative Stress and NO

1. Age-related EDD deficit is explained by reduced NO

2. Older adults can ameliorate NO mediated EDD by blocking oxidative stress

Aging increases vascular oxidative stress in B6D2F1 mice and suppress endothelial function.
Oxidative stress is bad: a twist in the Tale???


Chronic Inflammation as a Mechanism Contributing to Vascular Endothelial Dysfunction with Aging
Endothelium-dependent dilation relates to circulating C-reactive protein in middle-aged and older adults

Walker AE et al. *Hypertension* 2010;55:363-369
Vascular macrophage and T lymphocyte infiltration of aortas from young and old

Middle-aged and older adults with higher WBC count have impaired vascular function

Nuclear NFκB and inflammatory cytokines are increased in endothelial cells from older sedentary adults

Donato et al., Aging Cell, 2008
Reducing Nuclear NFκB signalling with 5 day Salsalate treatment improves endothelial dilation in older overweight sedentary adults
Modulators of Endothelial Function in Older Adults

1. **Physical Inactivity** Desouza et al. 2000 Tadei et al. 1999
2. **Blood pressure** Taddei et al. 1995
3. **LDL cholesterol** Walker et al. 2009
4. **Fasting Glucose** DeVan et al. 2013
5. **Sodium intake** Jablonski et al. 2009
6. **WBCs** Walker et al. 2010
7. **Norepinephrine** Kaplon et al. 2011

**with advancing age post prandial clearance of elevated glucose and lipids decreases significantly even in healthy adults (Basu et al. 2006, Issa et al. 2005).**

Thus, it is a tenable hypothesis that this post prandial state underlies the vascular aging phenotype since endothelial culture studies suggest that physiological elevations in glucose and lipids induce oxidative stress and inflammation and also negatively alter “Nutrient Sensitive” pathways Wu 2007, Chakrabarti 2009, Mortuza 2013
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Longevity Nutrient Sensing Pathways

• Sirtuin activators (STACs)
• AMPK (AICAR)
• TOR inhibitor (Rapamycin)
Sirtuin Activating Compounds (STAC)

• Sir2 (*Silent information regulator 2*) exists in yeast, fruit fly and worm. SIRT-1 is the mammalian homologue. There are 7 sirituin genes

• A deacetylase

• The enzymatic activity is coupled to the energy status of the cell via the cellular NAD/NADH ratio

• Activation increases lifespan of mice

• Sirtuins have been implicated in the regulation of aging, transcription, apoptosis and stress resistance.
Aging results in blunted endothelial SIRT-1 expression and is associated with endothelial dysfunction

Can we reverse age-related changes by increasing SIRT1 activity with a small molecular activator SRT1720? (compliments of Sirtris Pharm.)
4 Weeks of SRT 1720 Treatment Restores EDD in Older Mice

**Also reduced arterial cytokine expression but did not improve NO bioavailability**

Gano et al. AJP Heart and Circ 2014
Summary

Aging

Metabolic Shifts

Genomic instability
Telomere attrition
Epigenetic alterations
Loss of proteostasis
Deregulated nutrient-sensing
Mitochondrial dysfunction
Cellular senescence
Inflammation
Oxidative Stress

Primary hallmarks
Causes of damage

Antagonistic hallmarks
Responses to damage

Integrative hallmarks
Culprits of the phenotype

Vascular Dysfunction
Thank You!

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Questions/comments