

June 26 - 30, 2023
Smolenice Castle, Slovakia

BenBedPhar Training School 2023

NRF2 in noncommunicable diseases:
From bench to bedside



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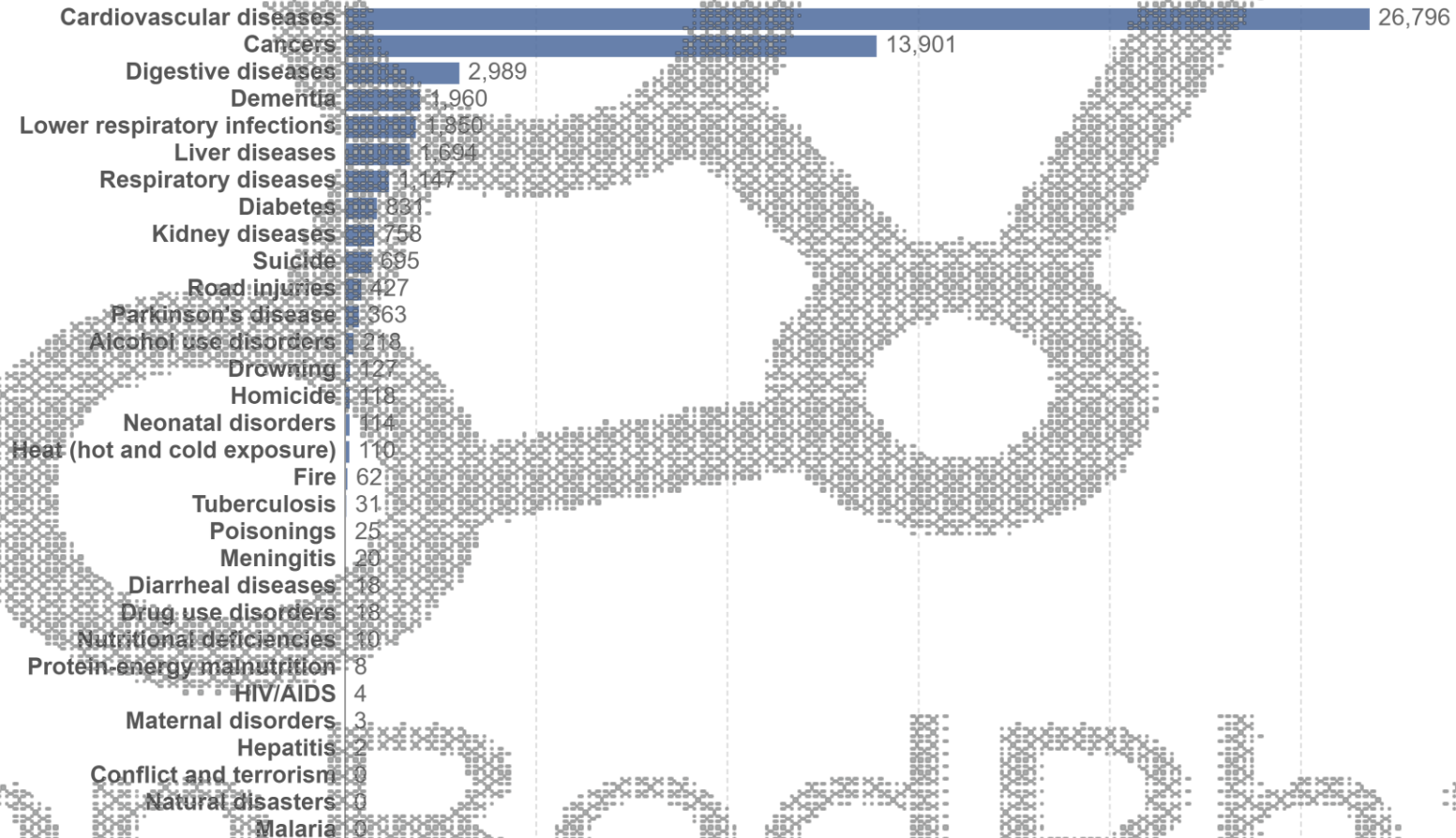
**NRF2 in CVDs:
a paradox box**

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Cardiovascular diseases (CVDs)

Number of deaths by cause, Slovakia, 2019

Our World
in Data

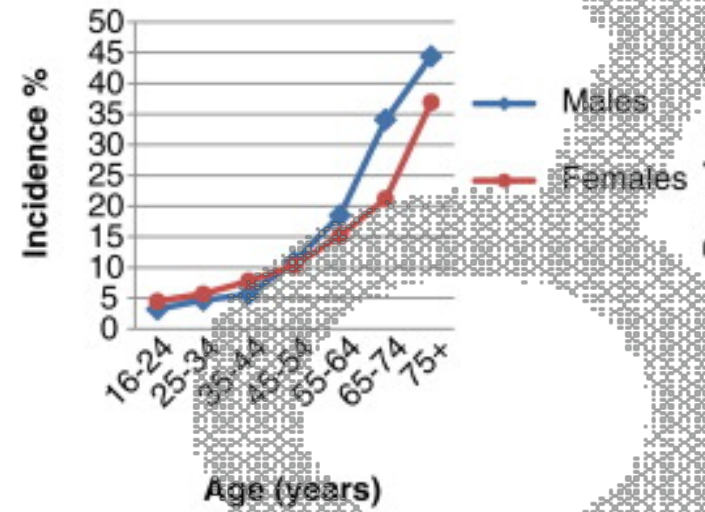


Source: IHME, Global Burden of Disease (2019)

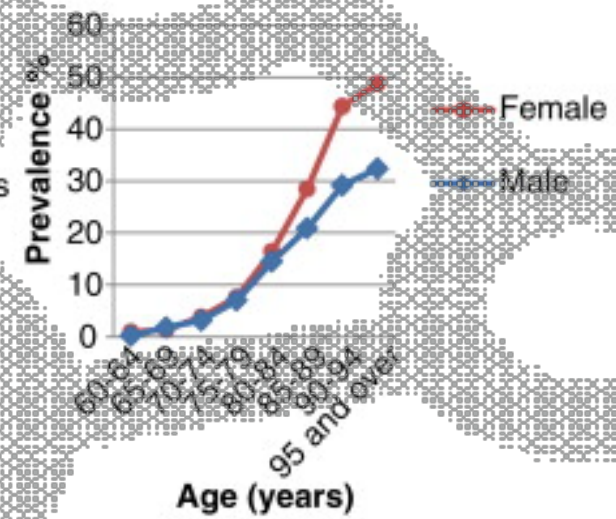
OurWorldInData.org/causes-of-death - CC BY

CVDs and ageing

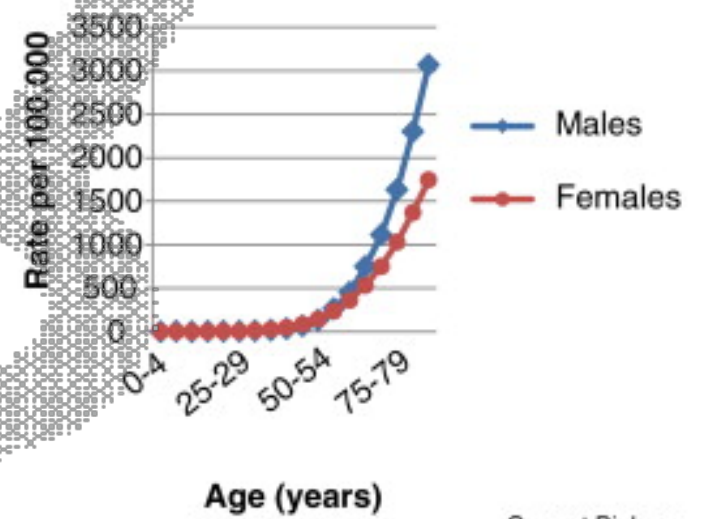
A England cardiovascular disease rates



B Europe dementia rates



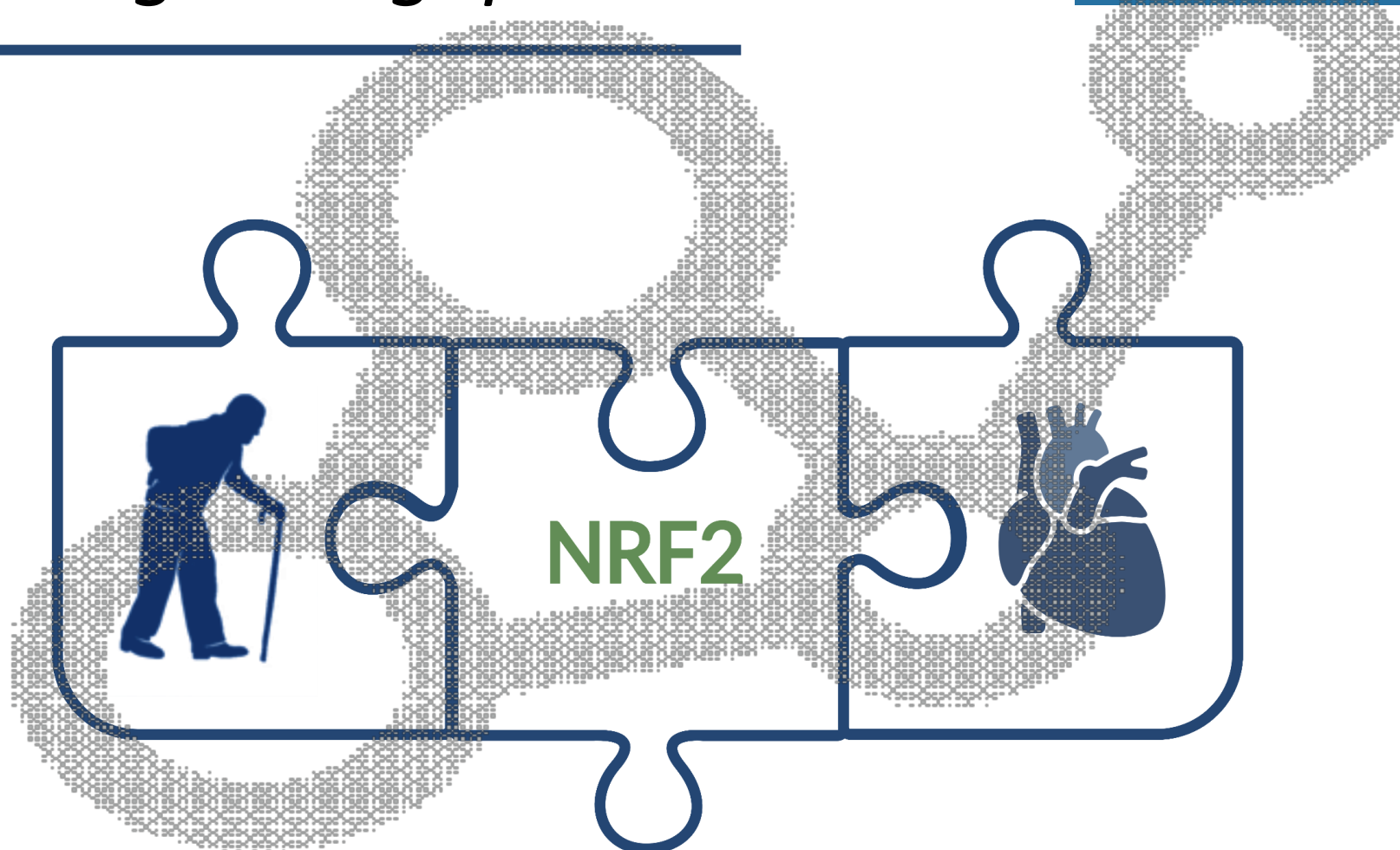
C UK cancer rates



Current Biology

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Can NRF2 bridge the gap?



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Harman's free radical theory of ageing

How are naked mole rats weird?



Cold-blooded mammals

Insect-like breeding colonies

Can survive up to 18 minutes without O₂

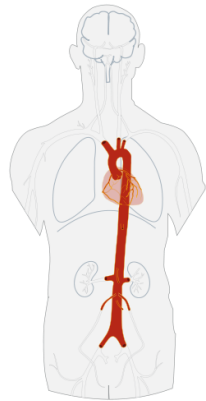
Lifespan >30 years

Nrf2 level is 6-fold times higher than in wild-derived mouse

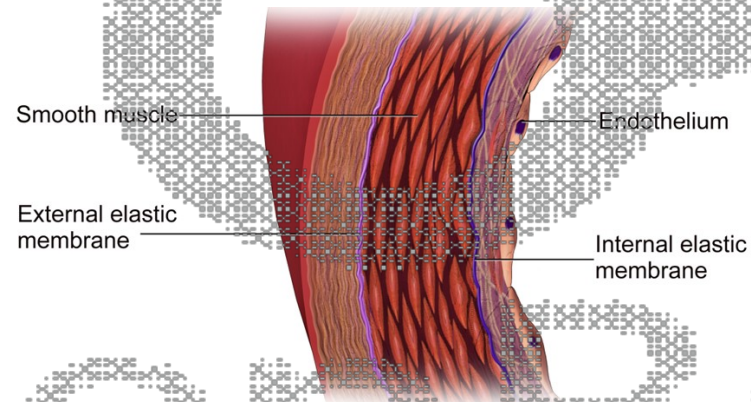
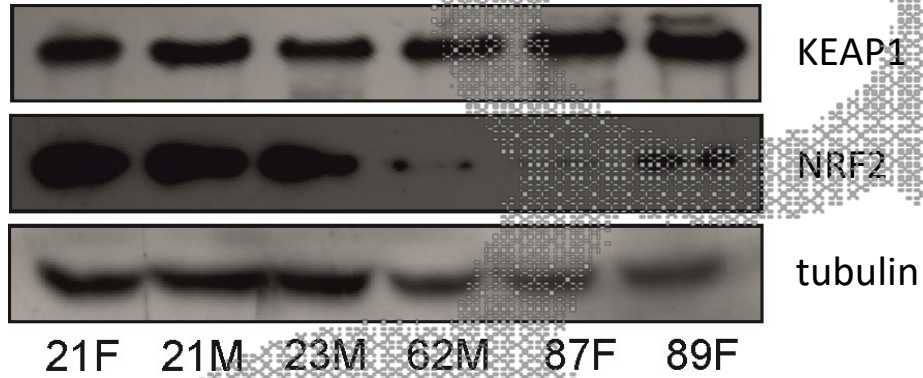
NRF2 activity (and level) declines in ageing

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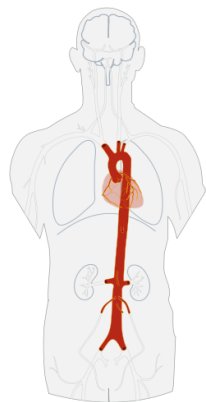
Nrf2 and vascular ageing crosstalk



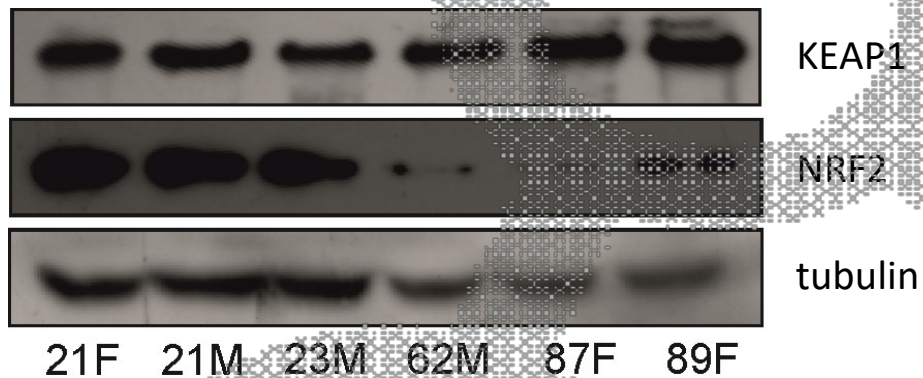
aortic ECs



Nrf2 and vascular ageing crosstalk

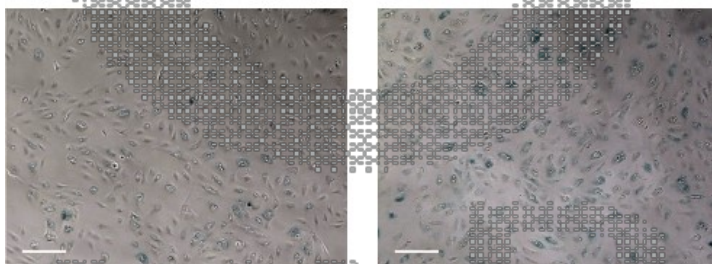


aortic ECs

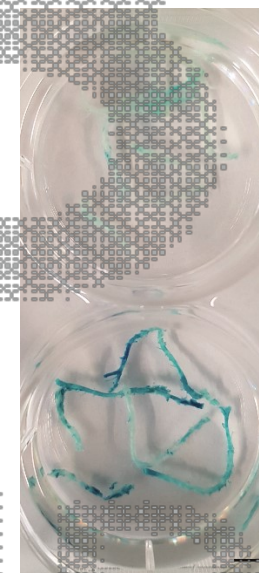


siMock

siNFE2L2



SA-β-gal activity pH 6

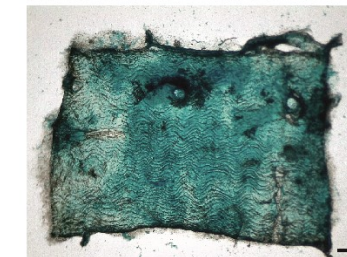


WT

tKO



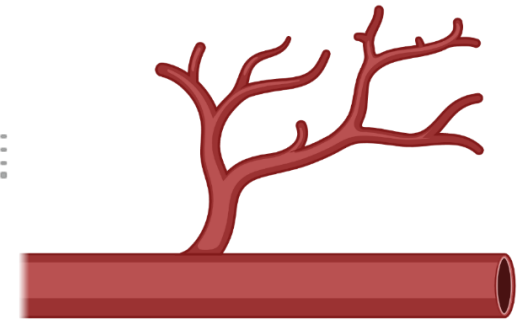
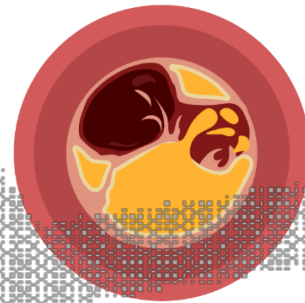
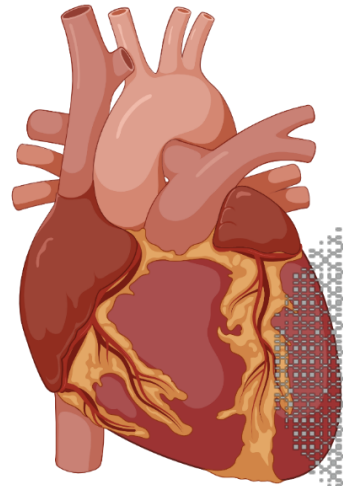
WT



tKO

SA-β-gal activity pH 6

NRF2 in CVDs



heart failure

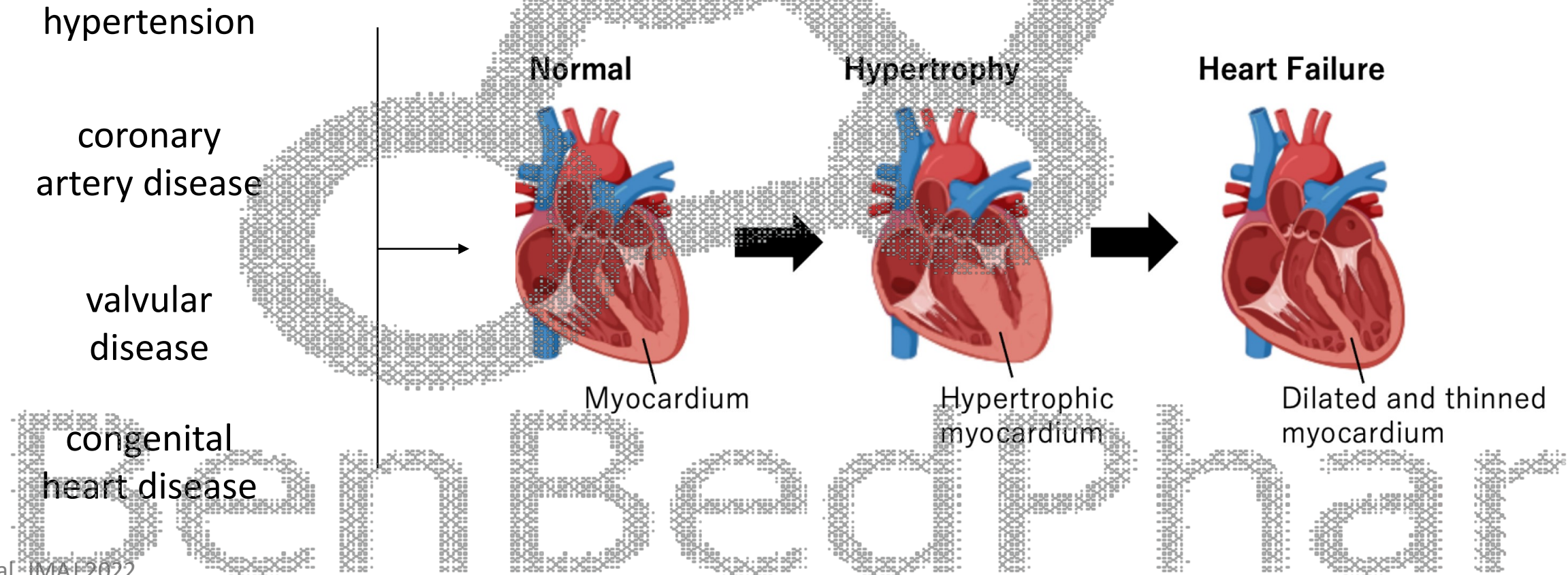
atherosclerosis

ischemia

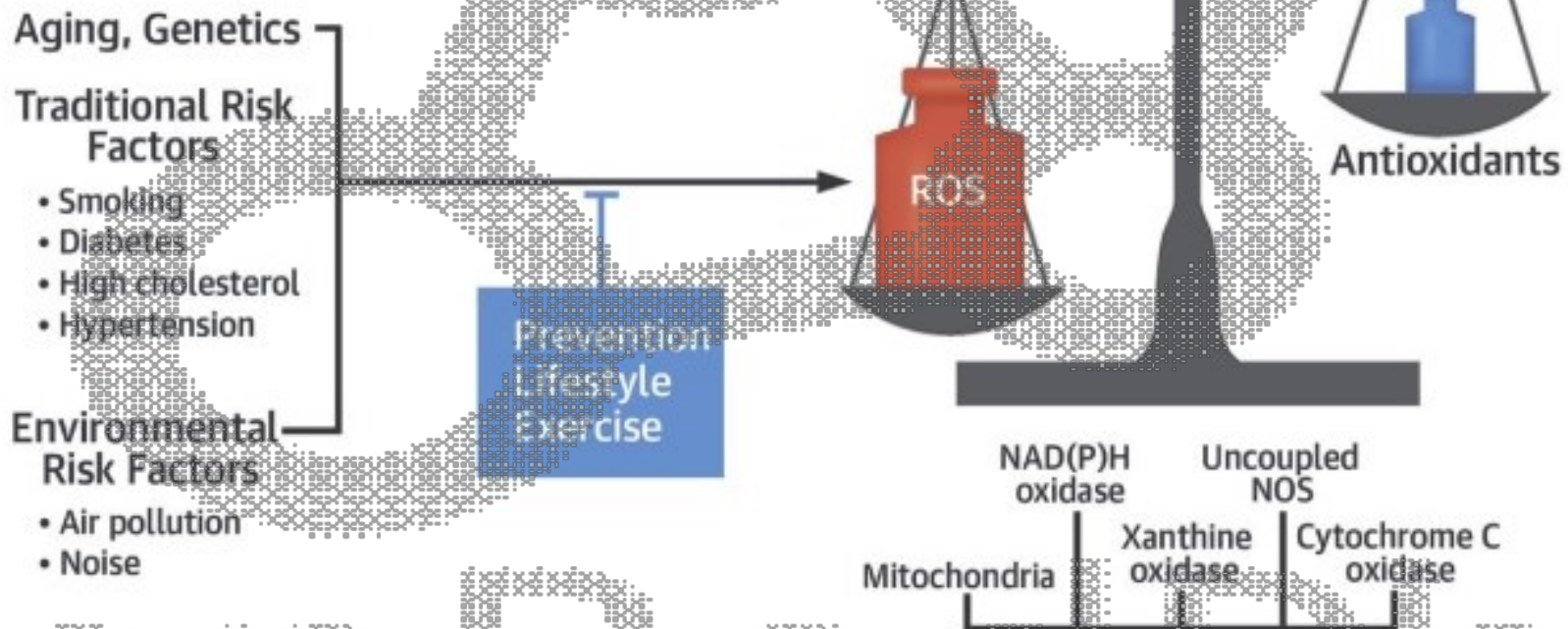
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Heart failure

A cardiac disorder, of any etiology, that impairs the ability of the ventricle to fill with or eject blood



Heart failure and ROS



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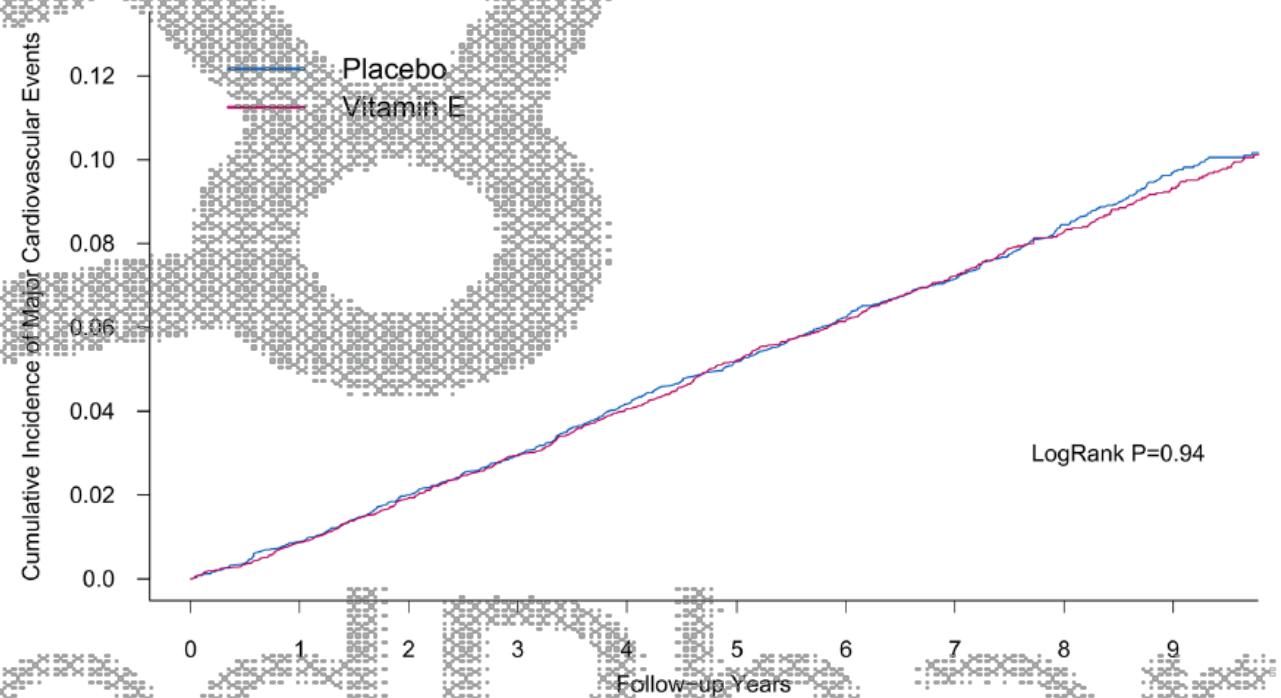
antioxidant vitamin use as an adjunct therapy



14 641 randomized male patients
10-year follow-up
major cardiovascular events
400 IU vitamin E every other day
500 mg vitamin C daily

Compared with placebo, vitamin E had **no effect** on the incidence of major cardiovascular events, as well as total MI, total stroke, and **cardiovascular mortality**.

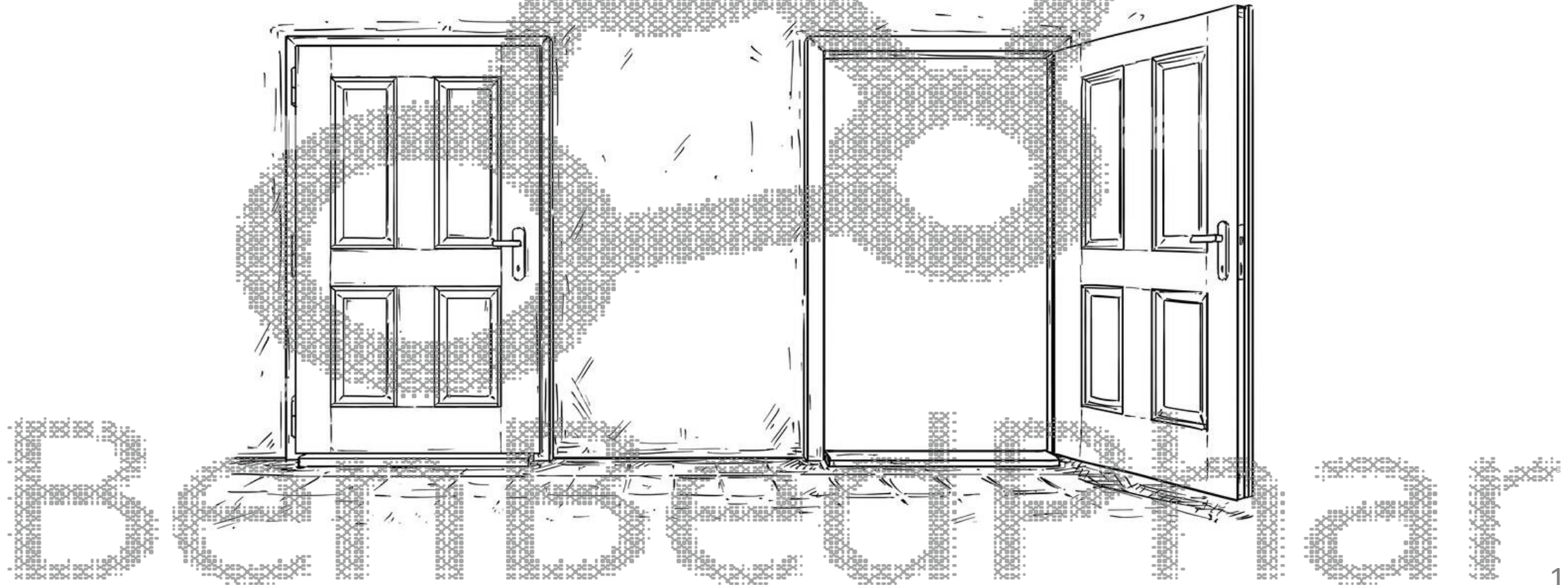
Vitamin E was associated with an **increased risk of hemorrhagic stroke**.



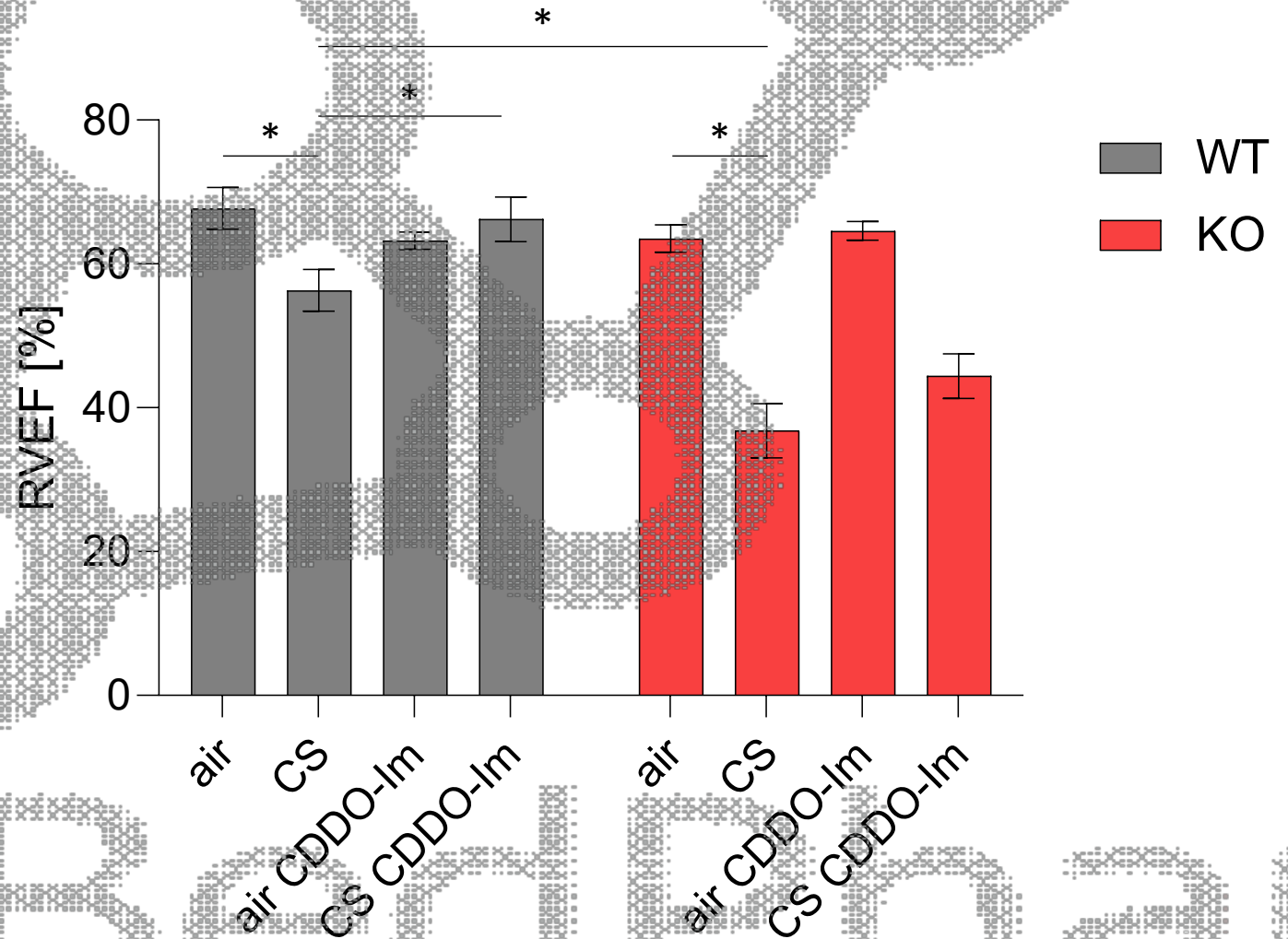
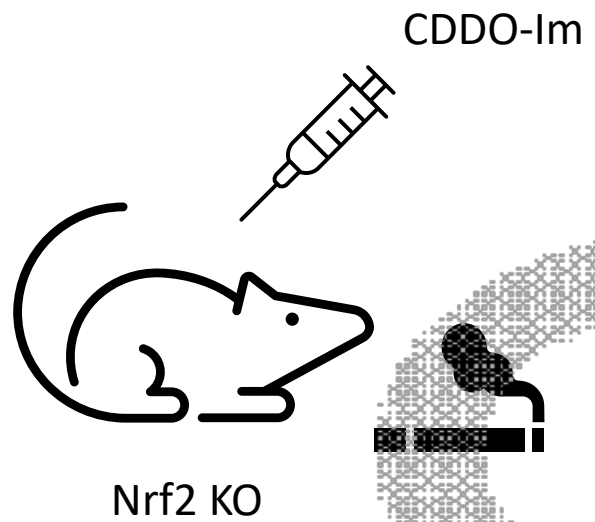
Take a different approach

antioxidants

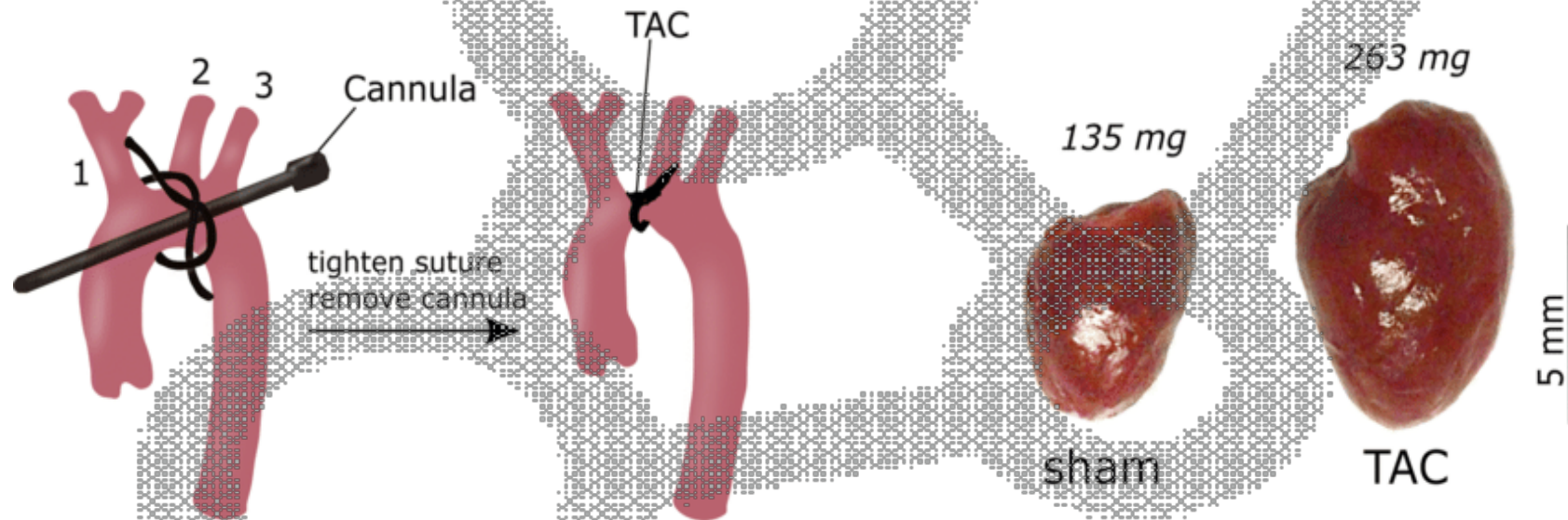
ROS sources
intrinsic antioxidant system



Cigarette smoke-induced cardiac dysfunction



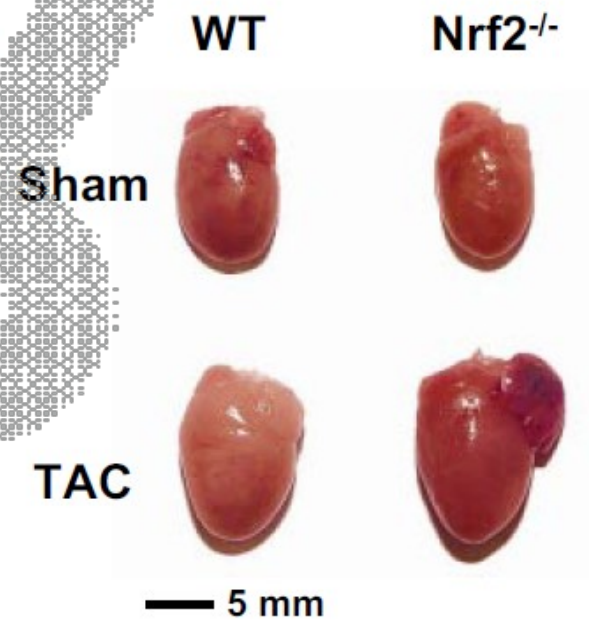
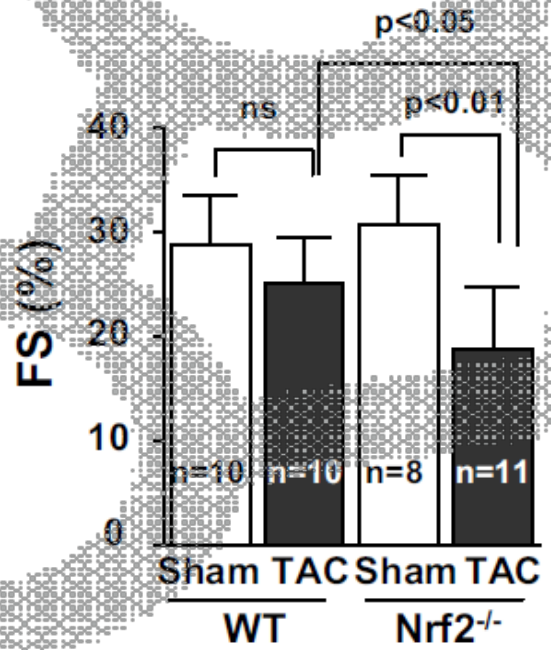
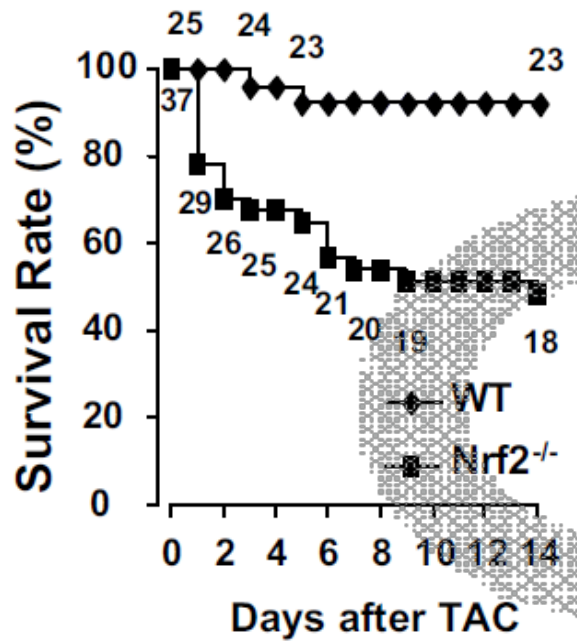
Pressure overload–induced cardiac hypertrophy



Transverse aortic constriction (TAC)

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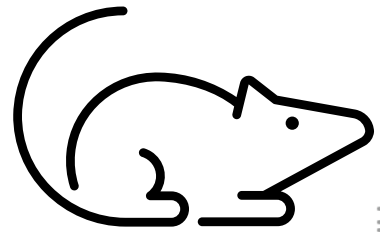
Pressure overload-induced cardiac hypertrophy



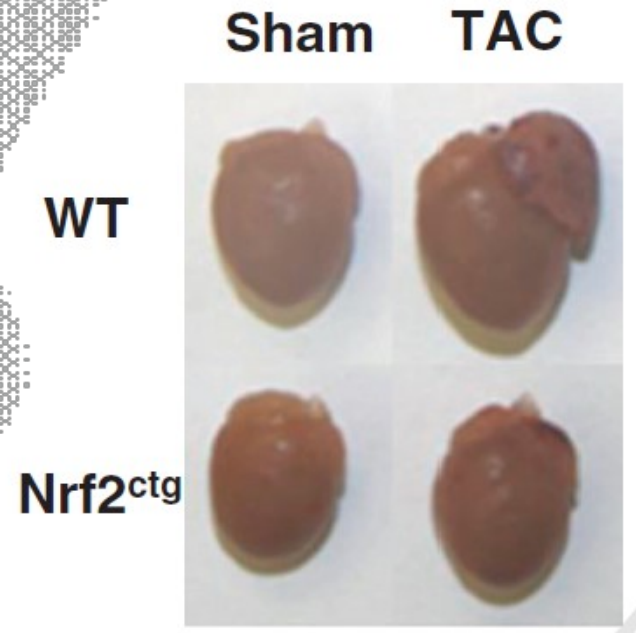
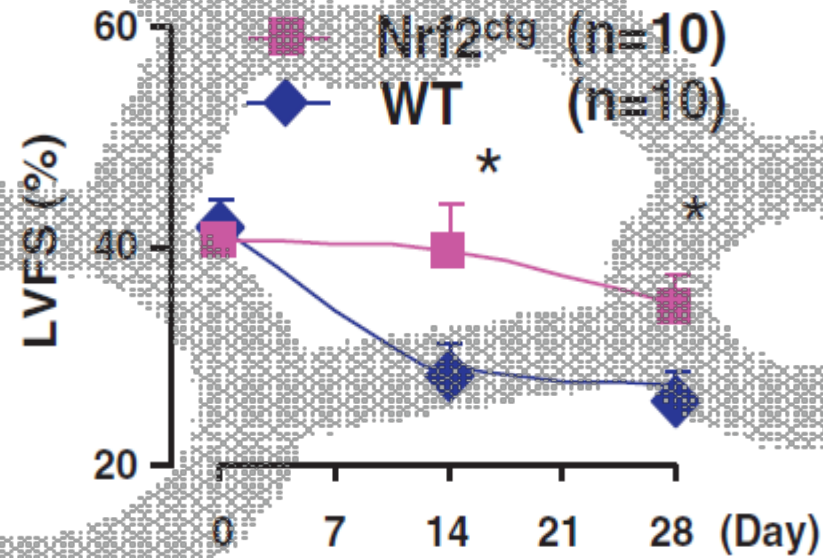
Left ventricle fractional shortening

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Pressure overload-induced cardiac hypertrophy

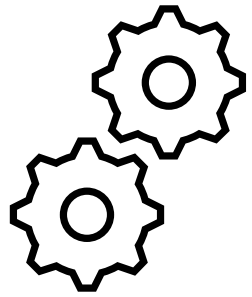


Cardiomyocyte Nrf2
overexpression

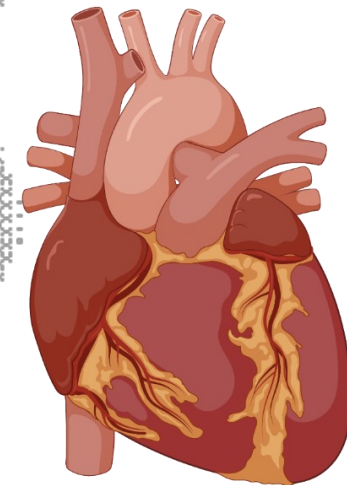


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NRF2 cardioprotection

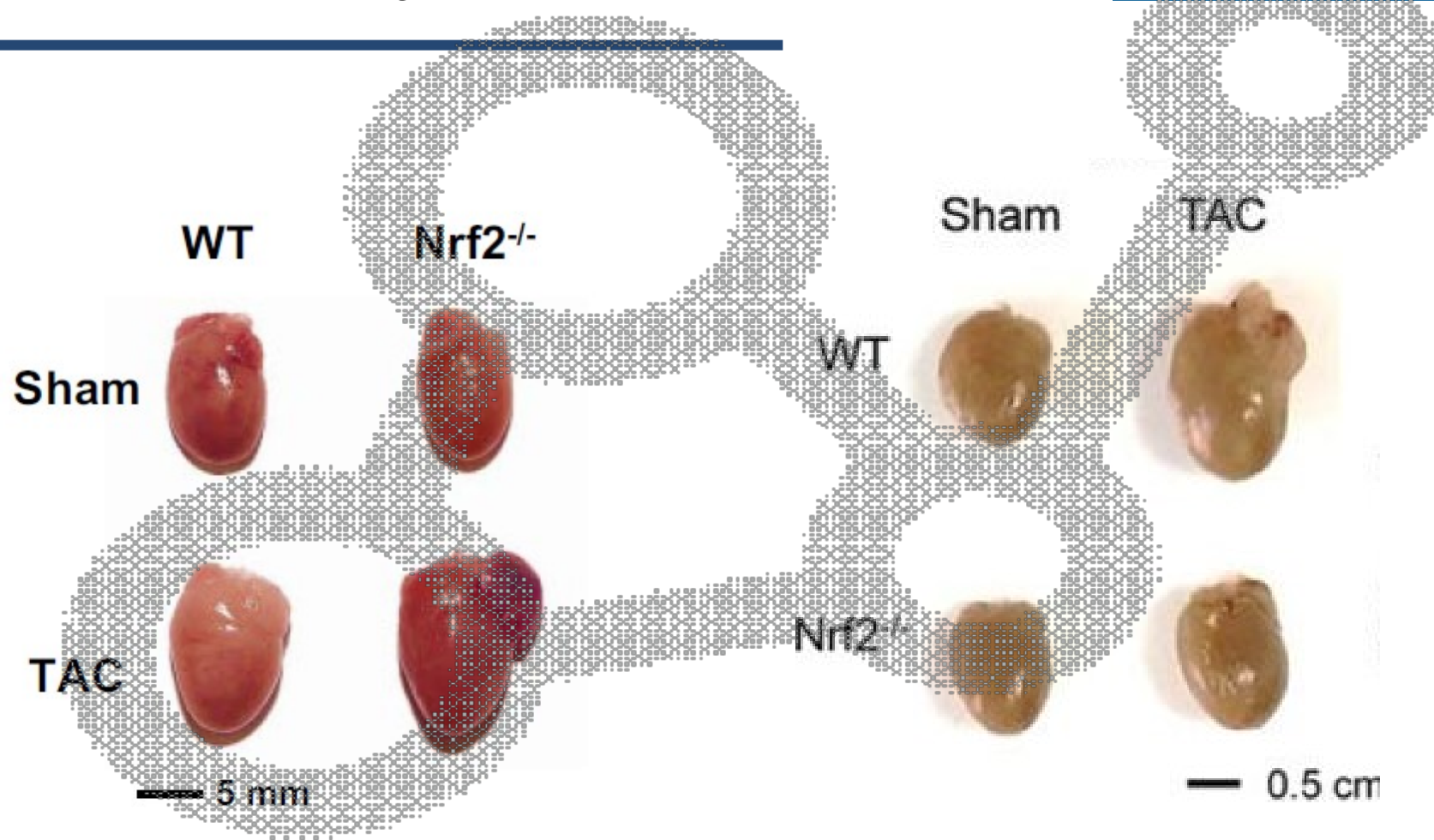


- Activation of antioxidant defence
- Metabolism regulation
- Protection from cell death
- Modulation of autophagy



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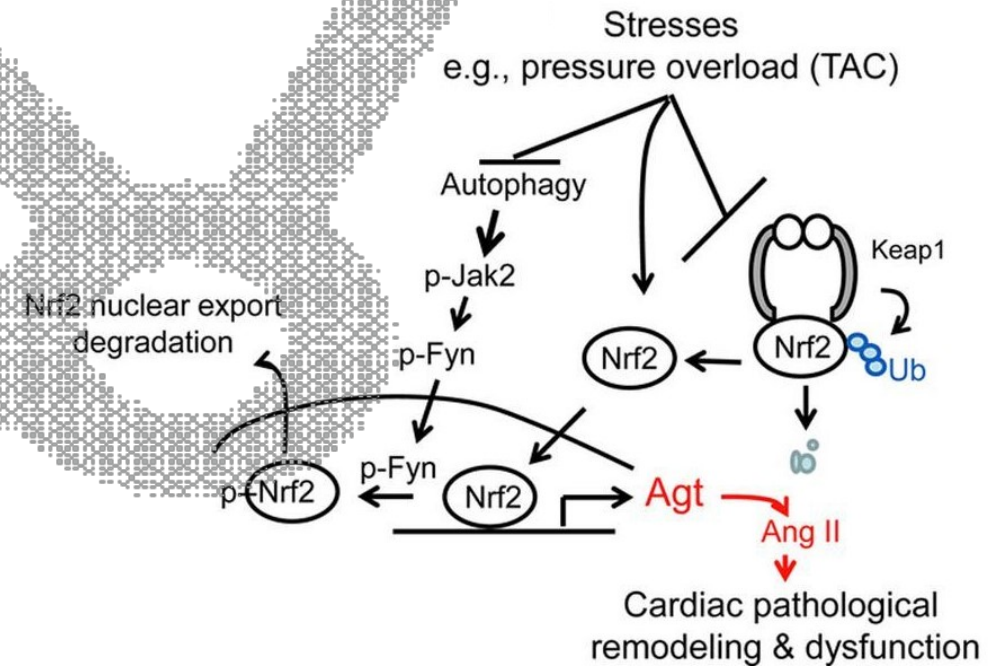
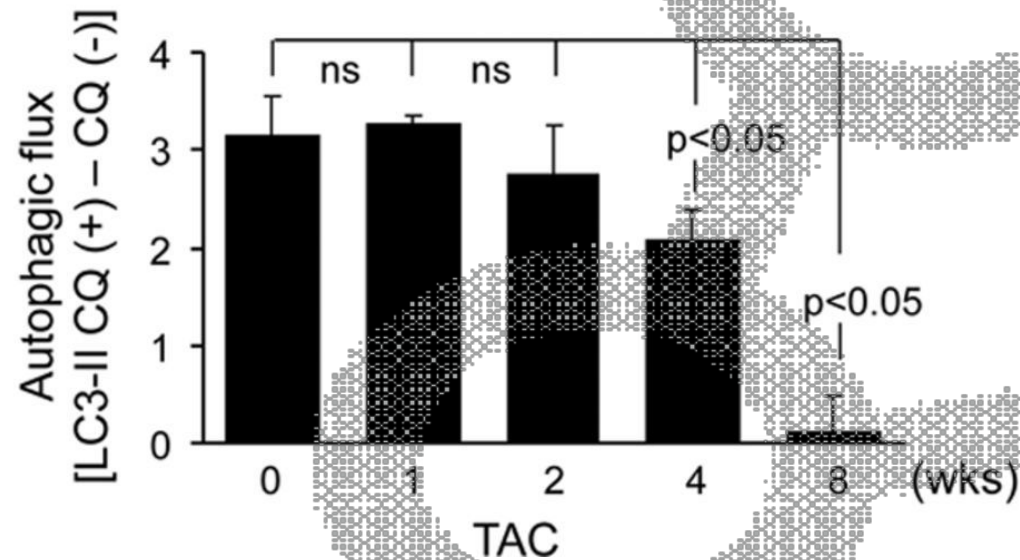
NRF2-dependent cardiac failure



2-weeks

4-weeks

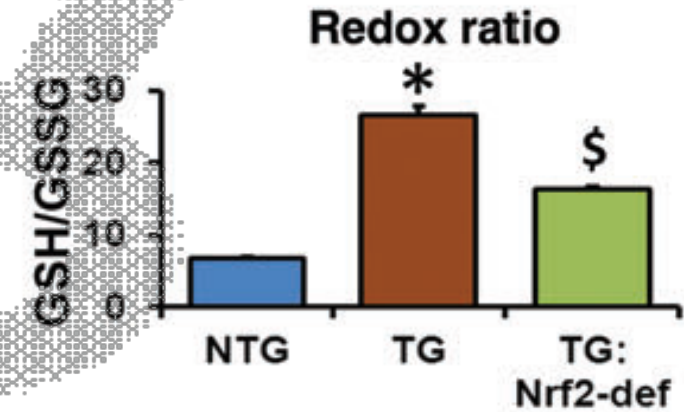
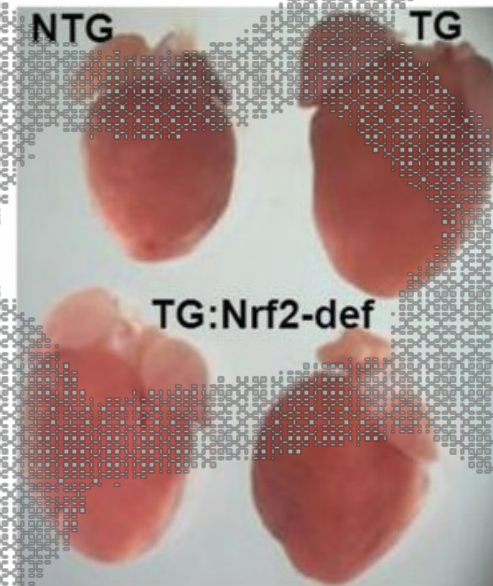
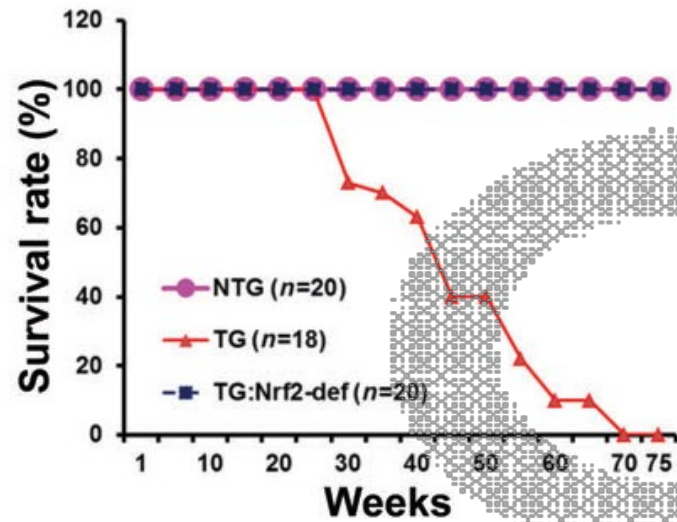
NRF2-dependent cardiac failure



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NRF2-dependent cardiac failure

CryAB overexpression – a cardiomyopathy model

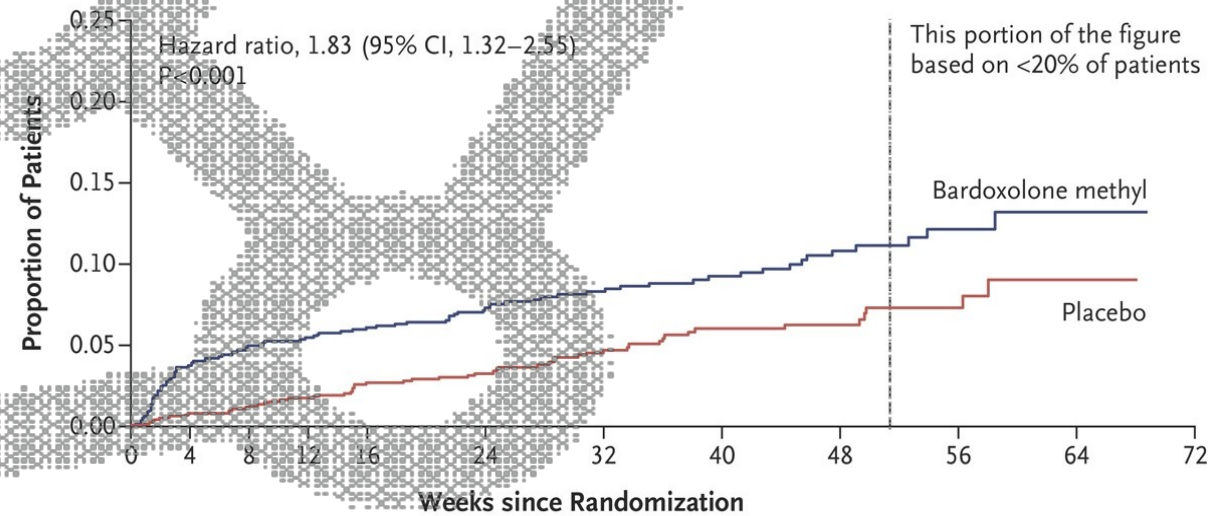


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NRF2 in heart failure



Heart Failure



No. at Risk

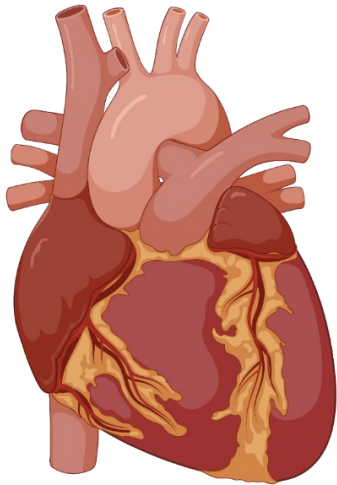
Bardoxolone methyl
Placebo

1088	1045	1006	942	864	723	548	417	288	133	15	0
1097	1089	1070	994	907	762	591	436	315	135	20	0

type 2 diabetes mellitus and stage 4 chronic kidney disease

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NRF2 and heart failure

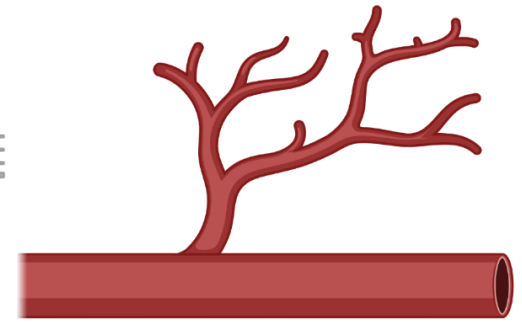
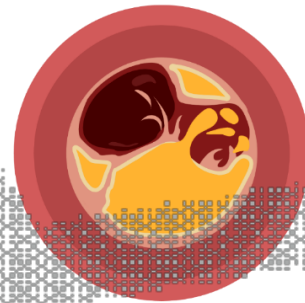
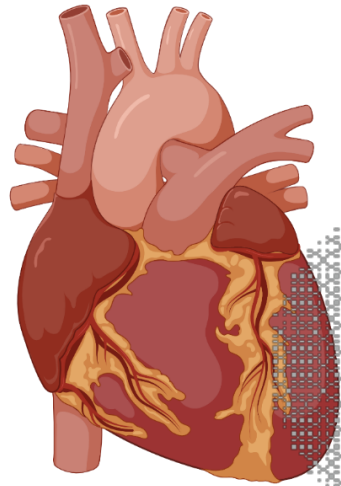


NRF2 deficiency can be protective or detrimental

Postulated discriminating factor: autophagy, reductive stress

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NRF2 in CVDs

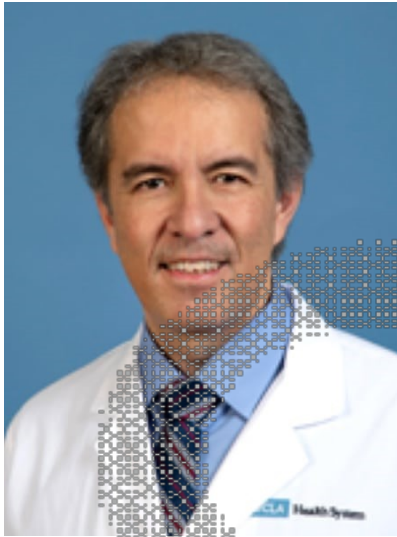


heart failure

atherosclerosis

ischemia

BenBedPhar

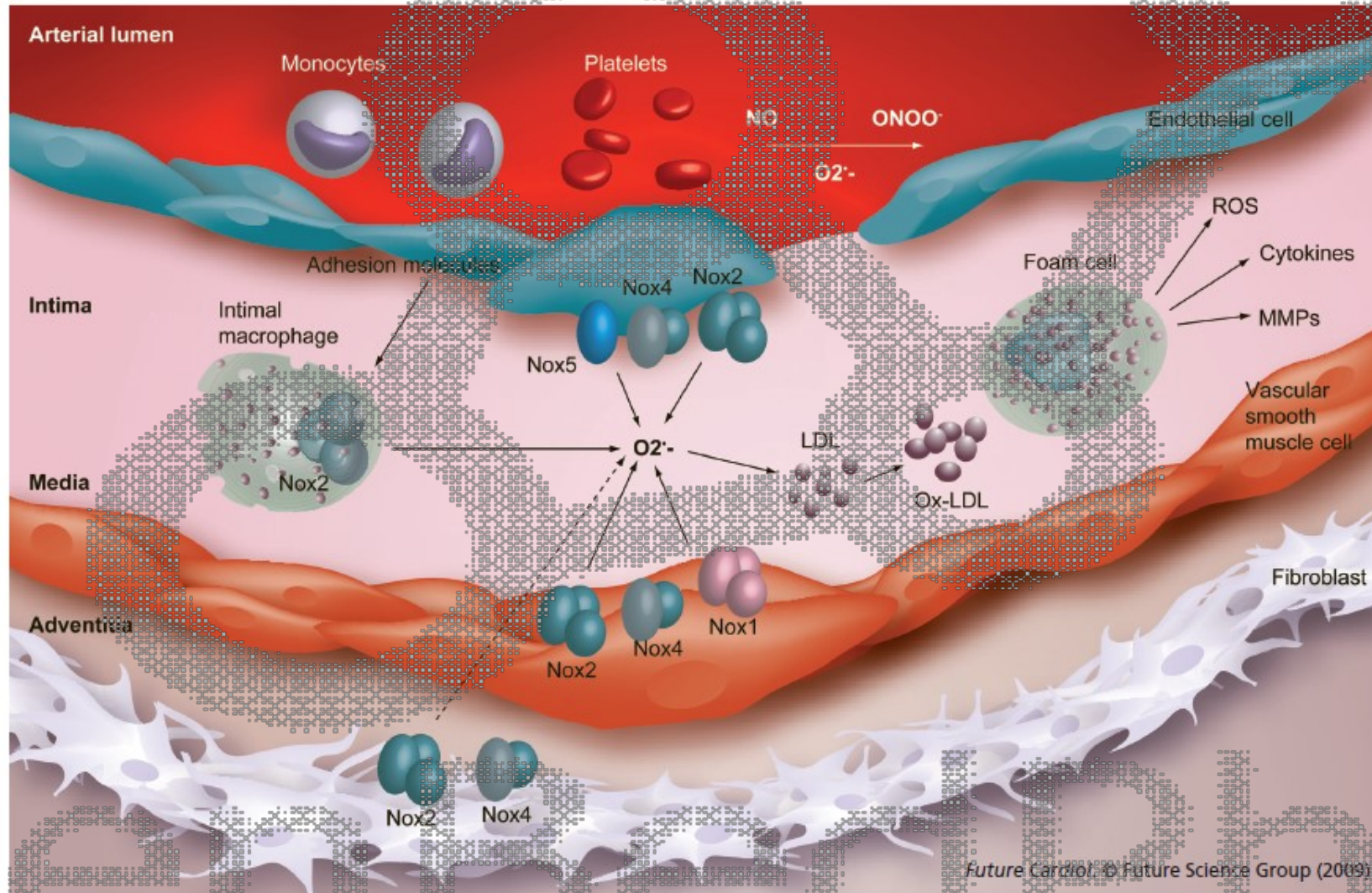


Jesus Araujo
UCLA

Nrf2 and the promotion of atherosclerosis:
lessons to be learned

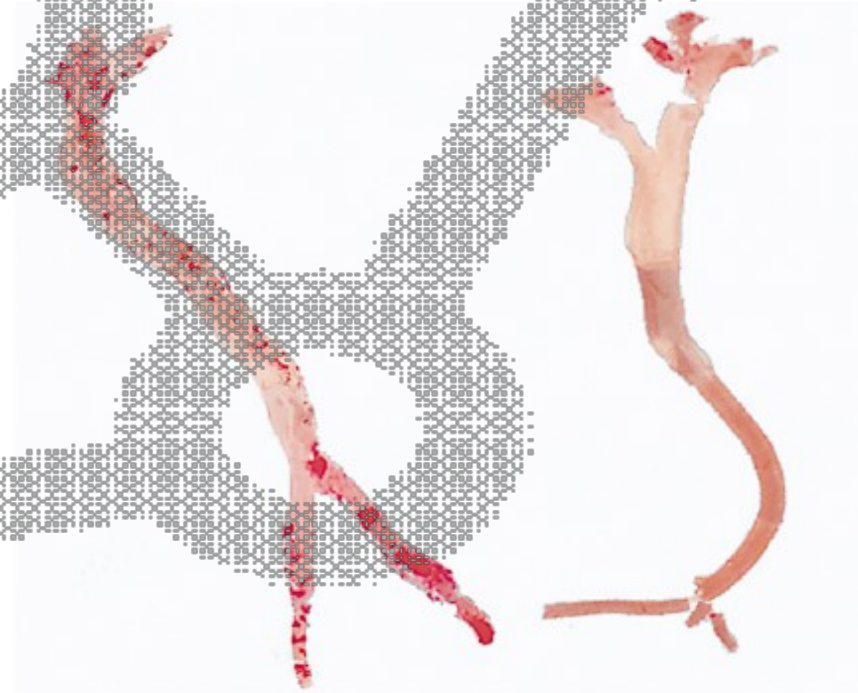
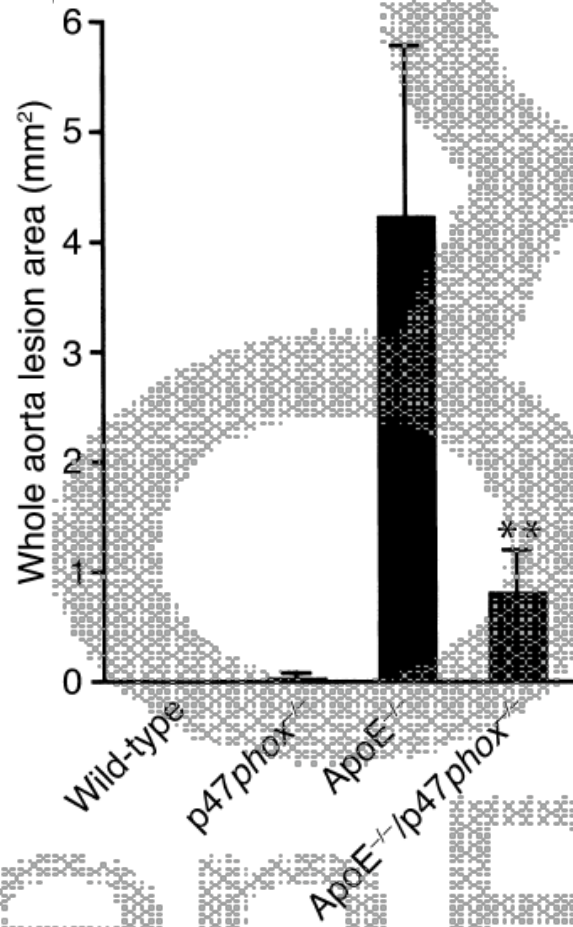
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NOX isoforms in the vessel wall



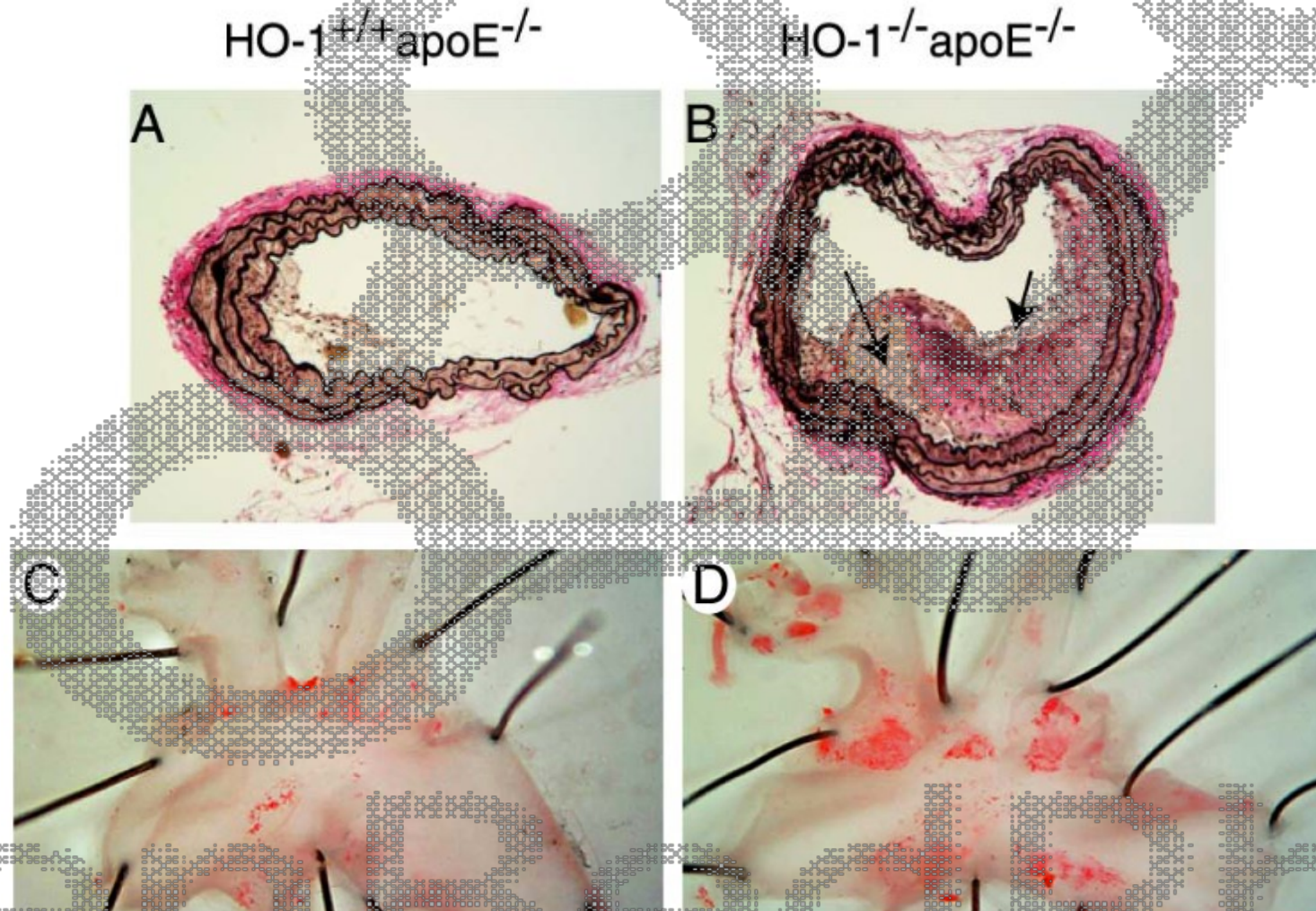
Future Cardiol. © Future Science Group (2009)

Deficiency of p47phox subunit



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Deficiency of HO-1

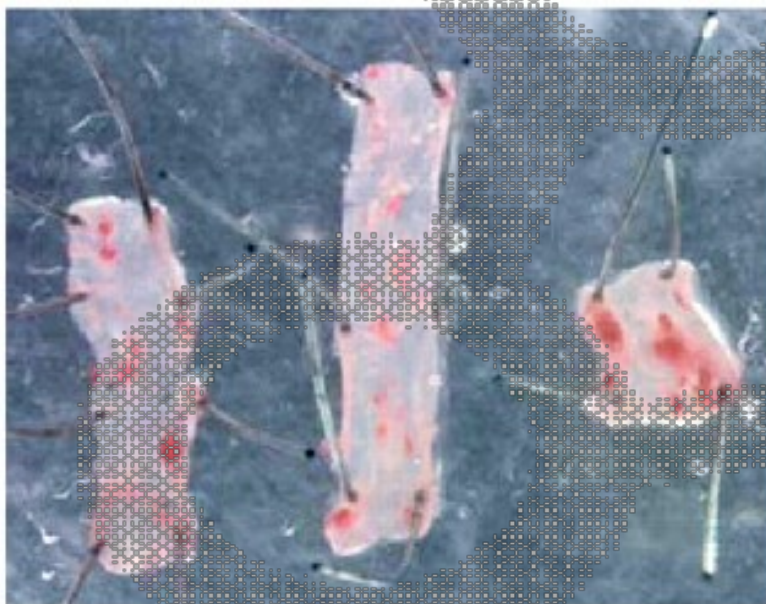


Deficiency of GPx-1

Diabetic ApoE-/-

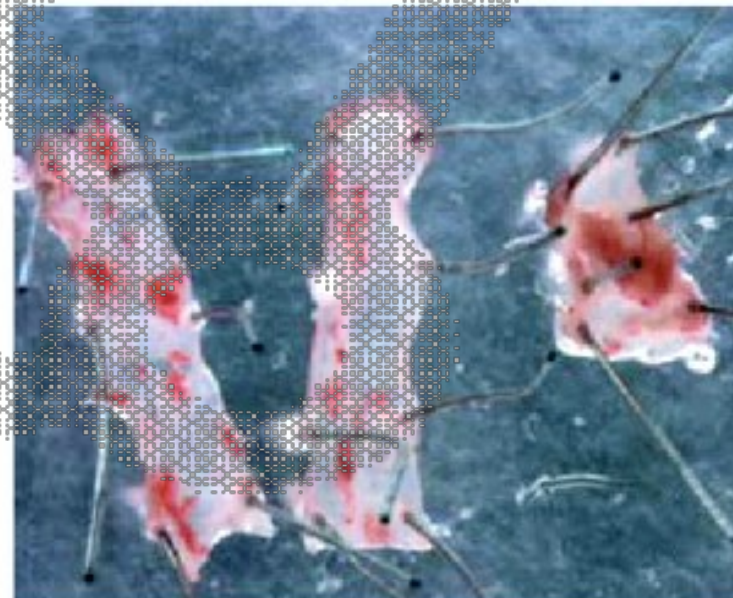
Diabetic ApoE-/- GPx-1-/-

C



Abdominal Thoracic Arch

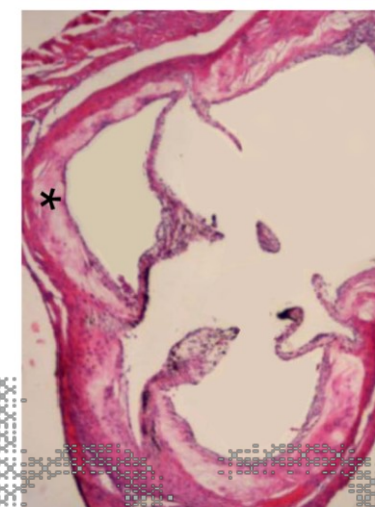
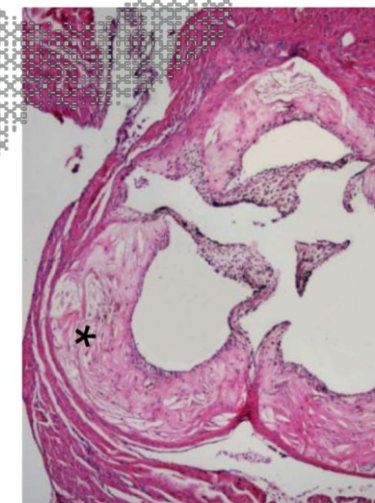
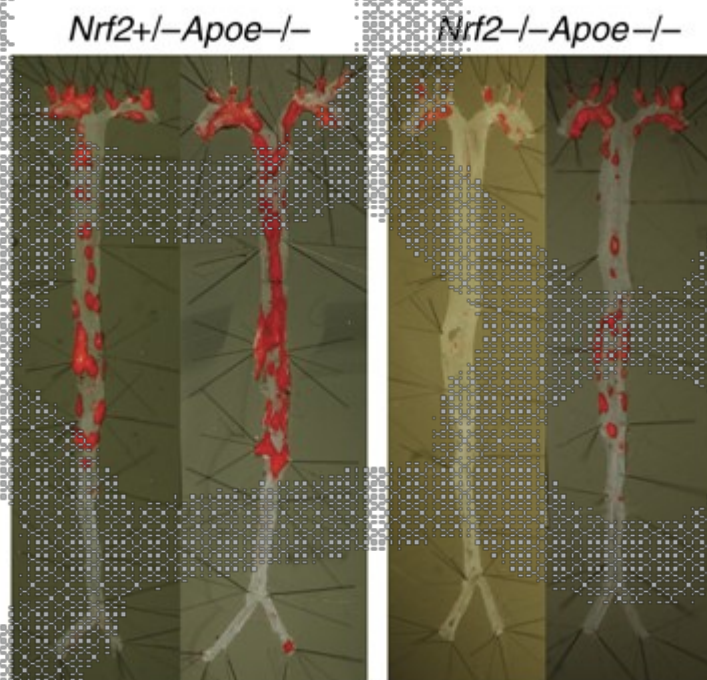
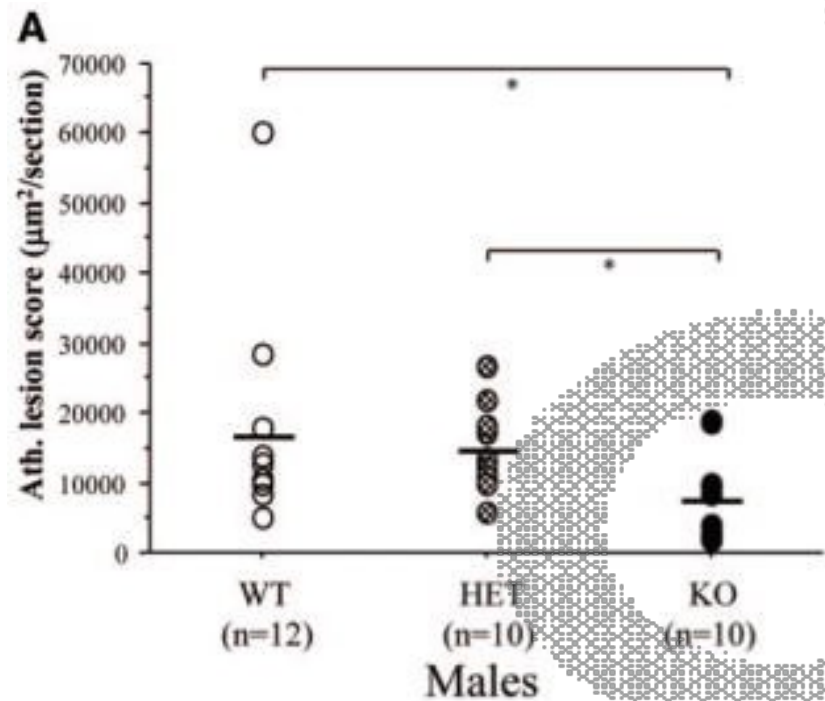
D



Abdominal Thoracic Arch

BenBedPhar

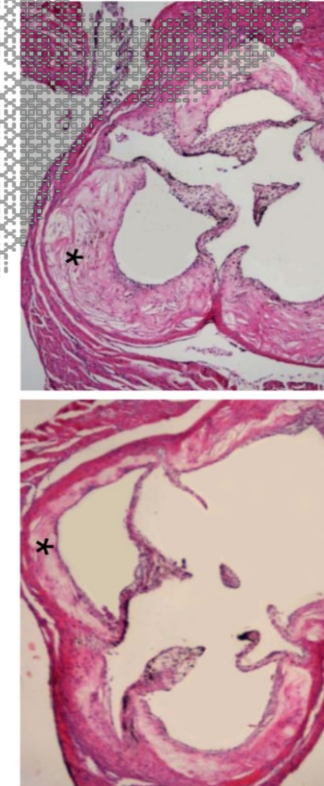
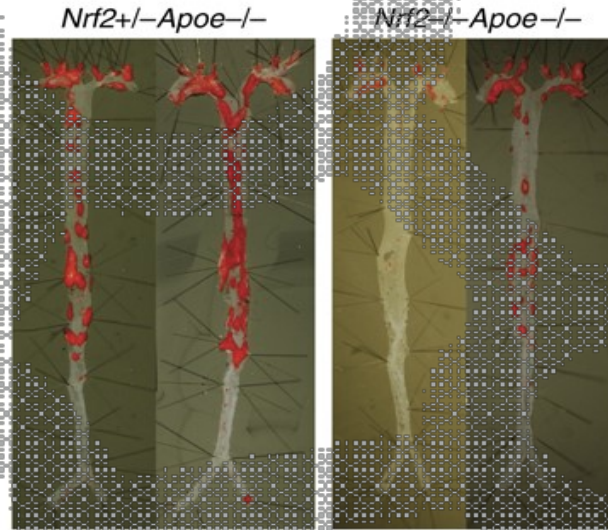
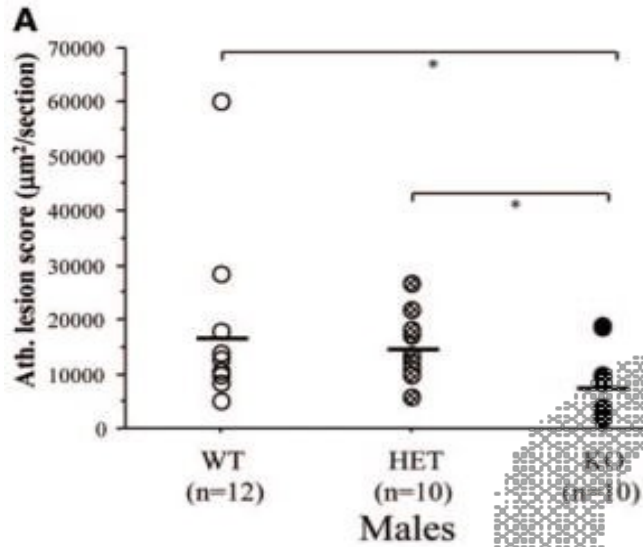
Deficiency of NRF2



ApoE^{-/-}

ApoE^{-/-}
Nrf2^{-/-}

Deficiency of NRF2



ApoE-/-

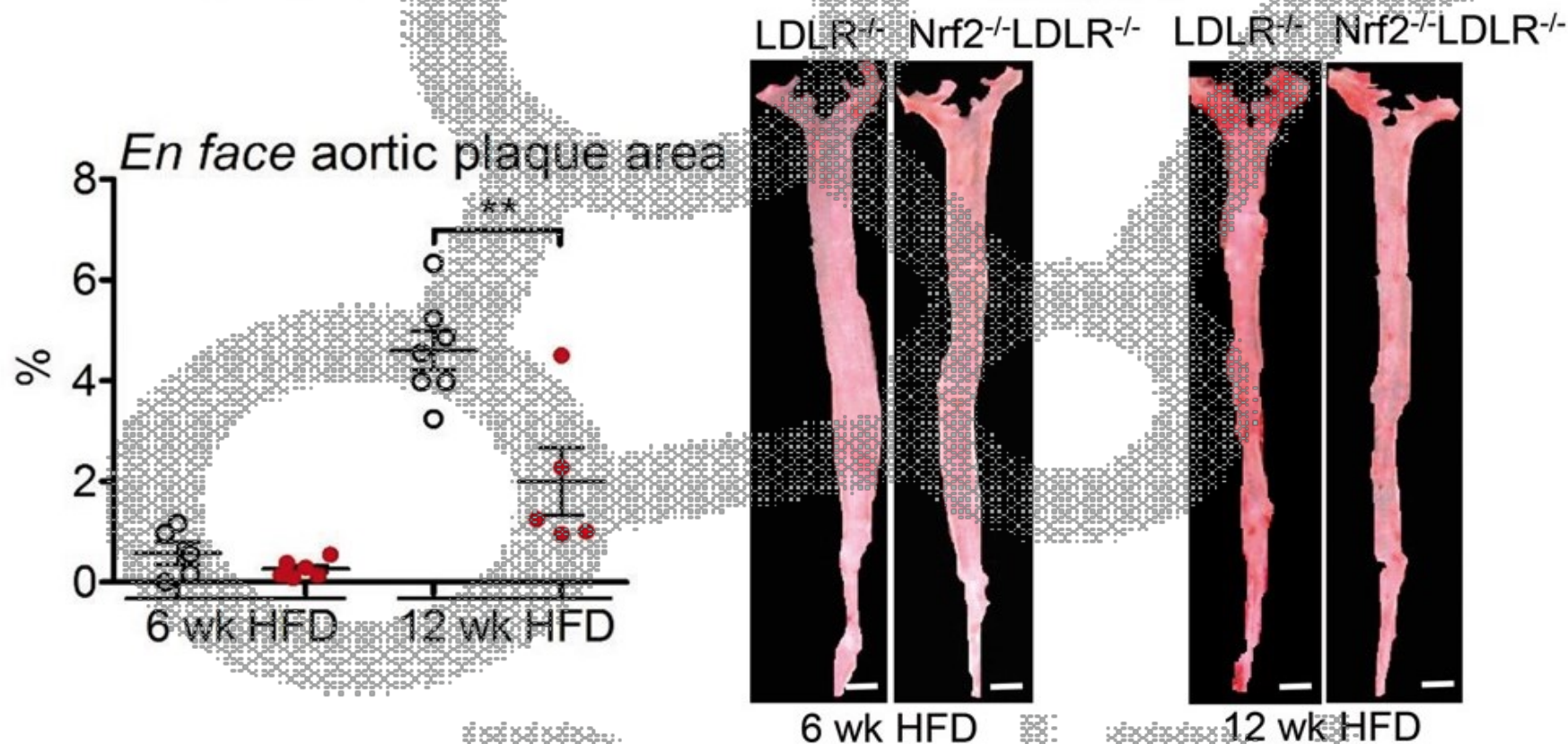
ApoE-/-
Nrf2-/-

lower plasma cholesterol
liver lipid metabolism
lower macrophage content

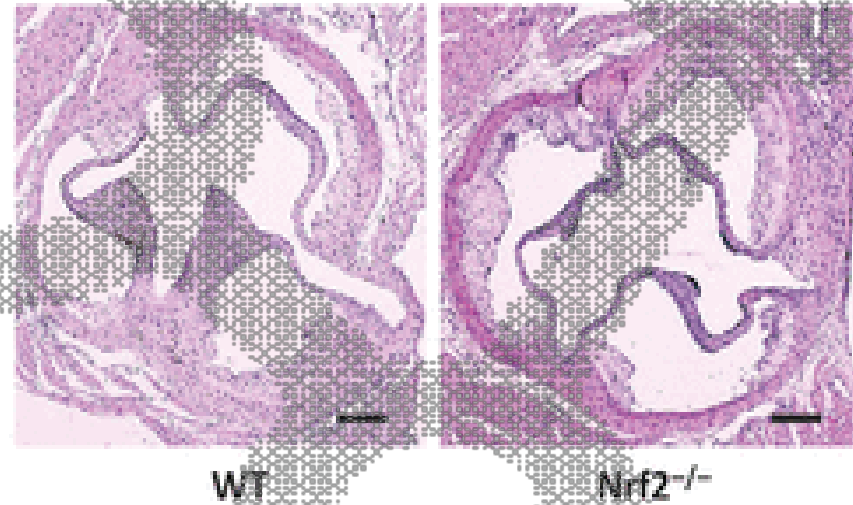
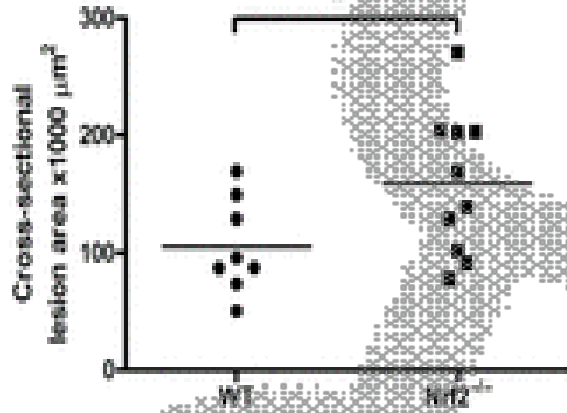
decreased IL-1-dependent
inflammation

decreased expression
of the scavenger receptor CD36

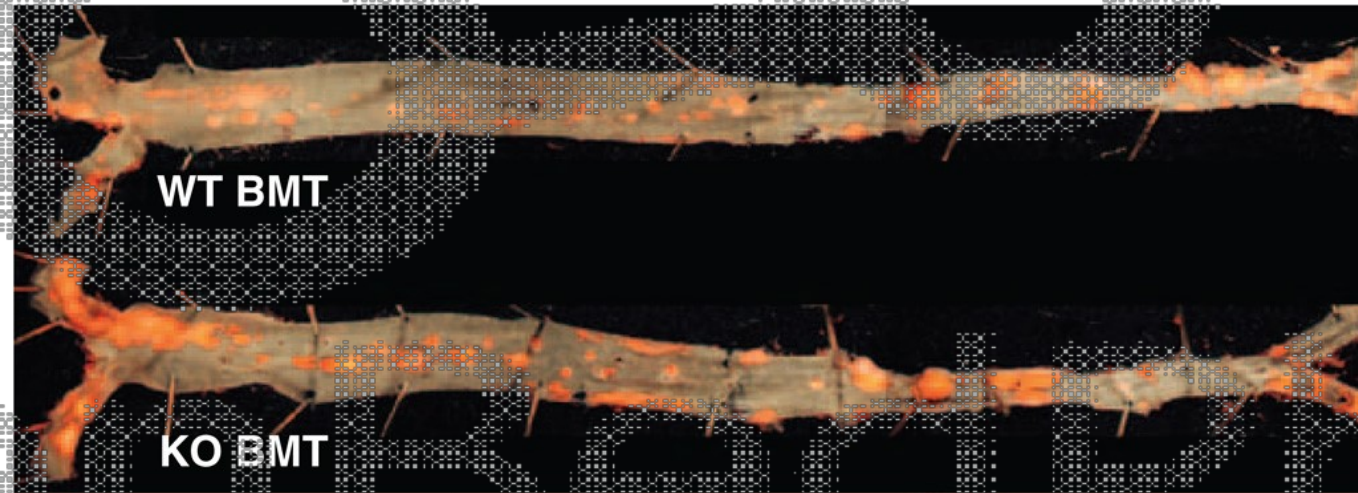
Deficiency of NRF2 in LDLR^{-/-}



Cell-specific deficiency of NRF2 - HSC



Early stage



Late stage

NRF2 and atherosclerosis

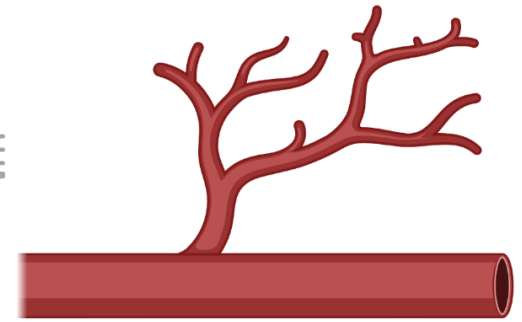
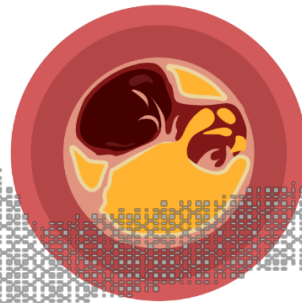
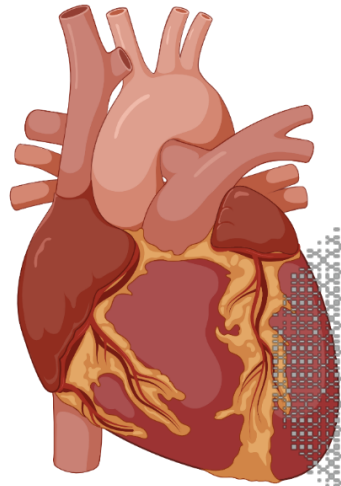


NRF2 deficiency can be protective or detrimental

Postulated discriminating factor: global or local NRF2 expression
and lipid metabolism

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NRF2 in CVDs



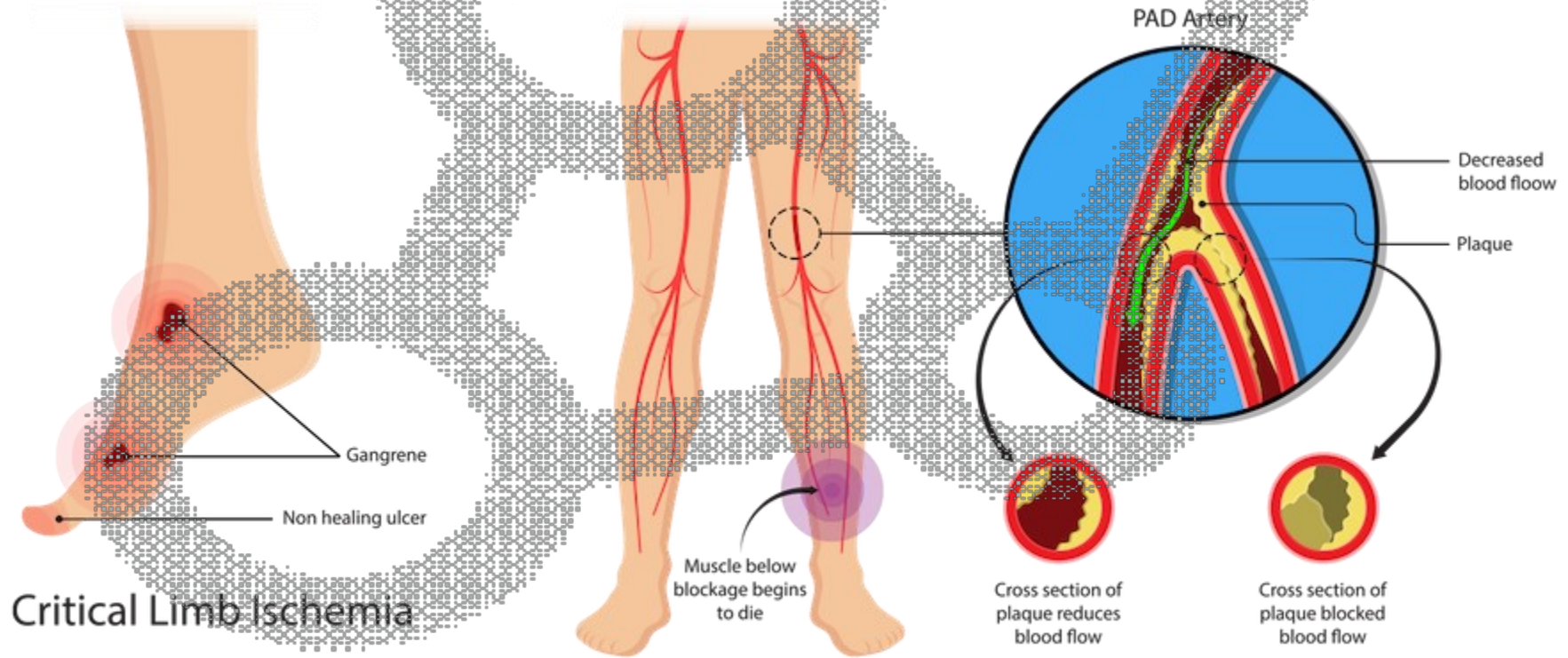
heart failure

atherosclerosis

ischemia

BenBedPhar

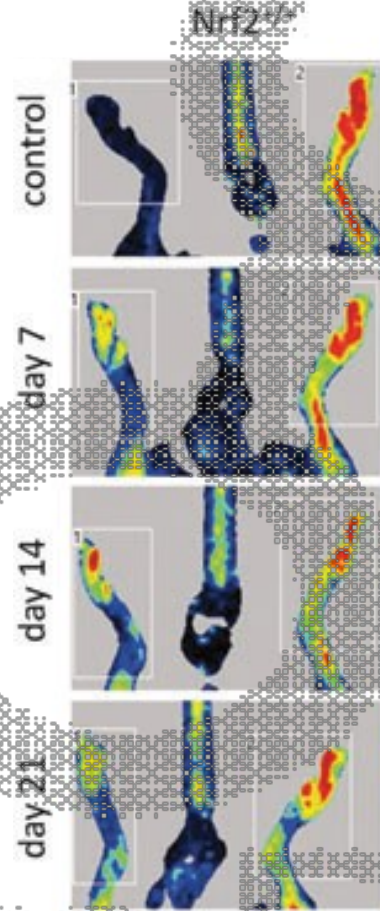
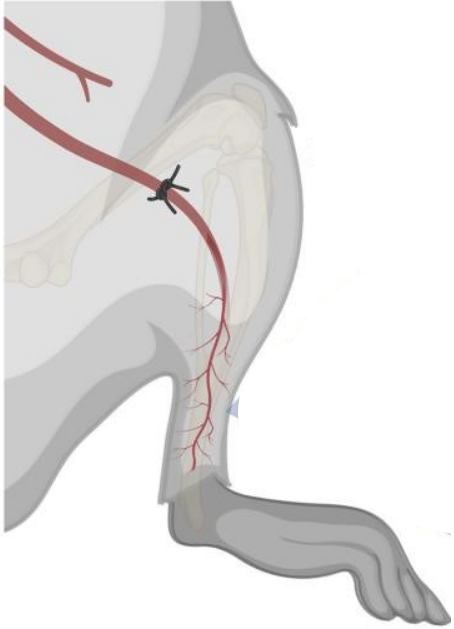
Peripheral arterial disease



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NRF2 in hind limb ischemia

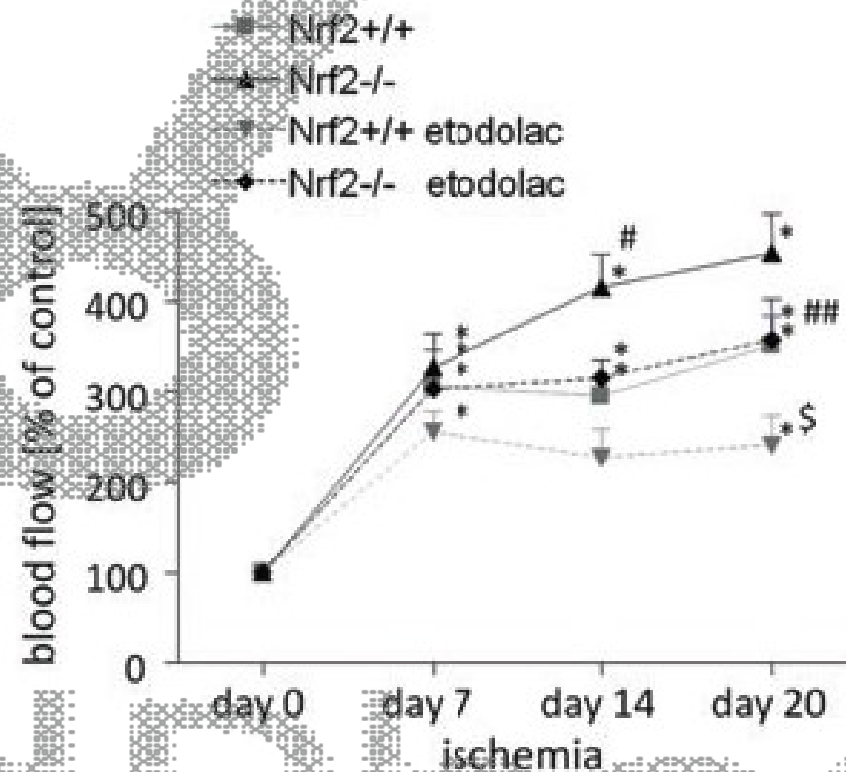
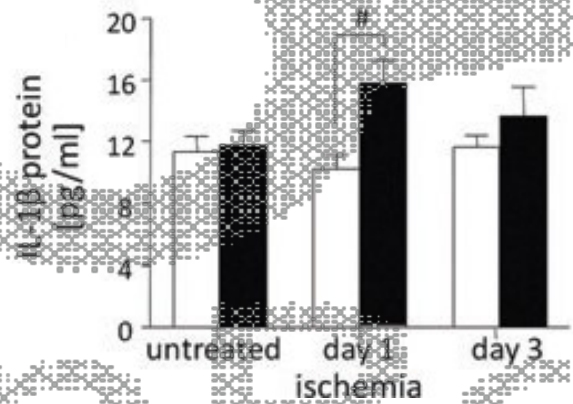
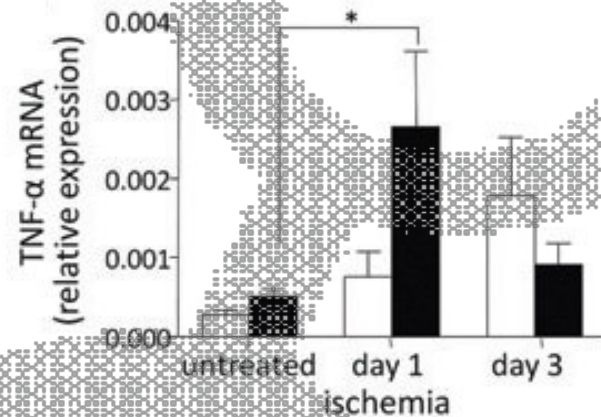
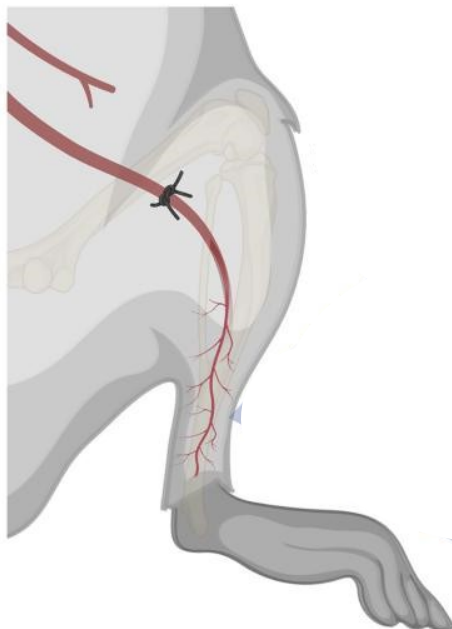
Femoral Artery Ligation



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NRF2 in hind limb ischemia

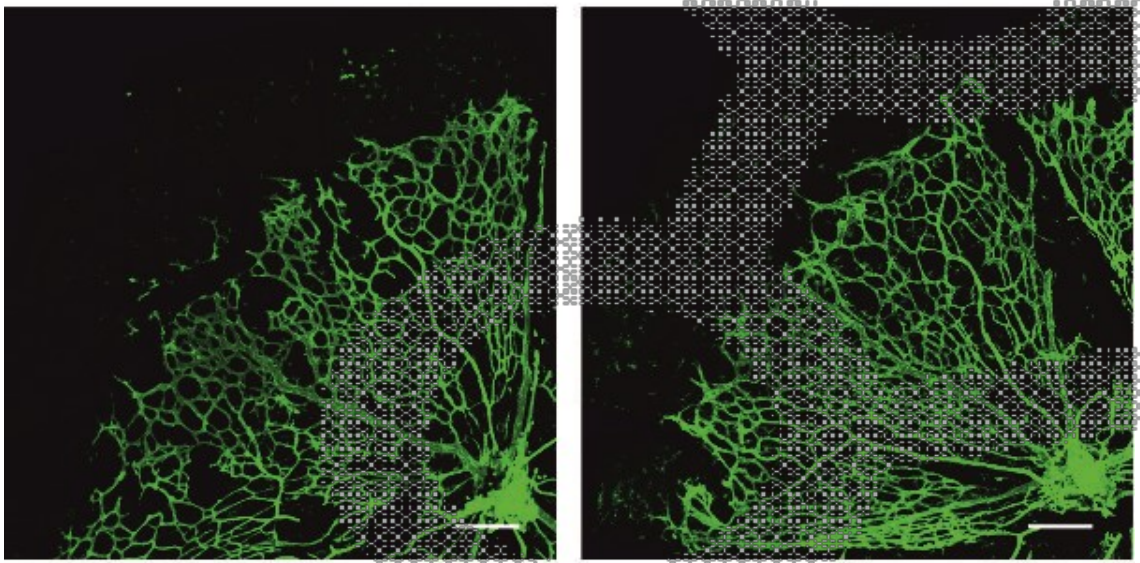
Femoral Artery Ligation



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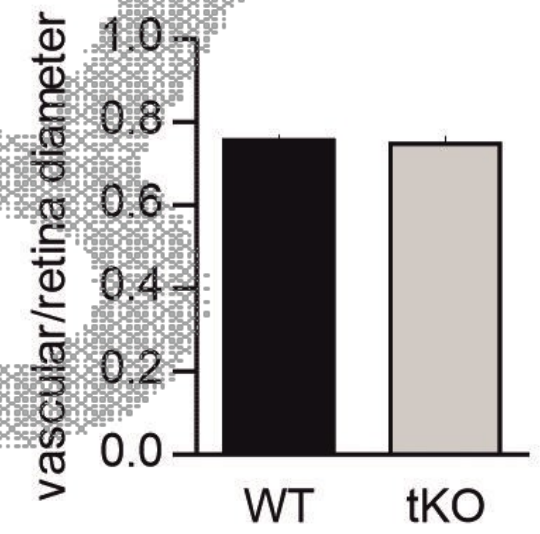
NRF2-dependent angiogenesis

isolectin B4



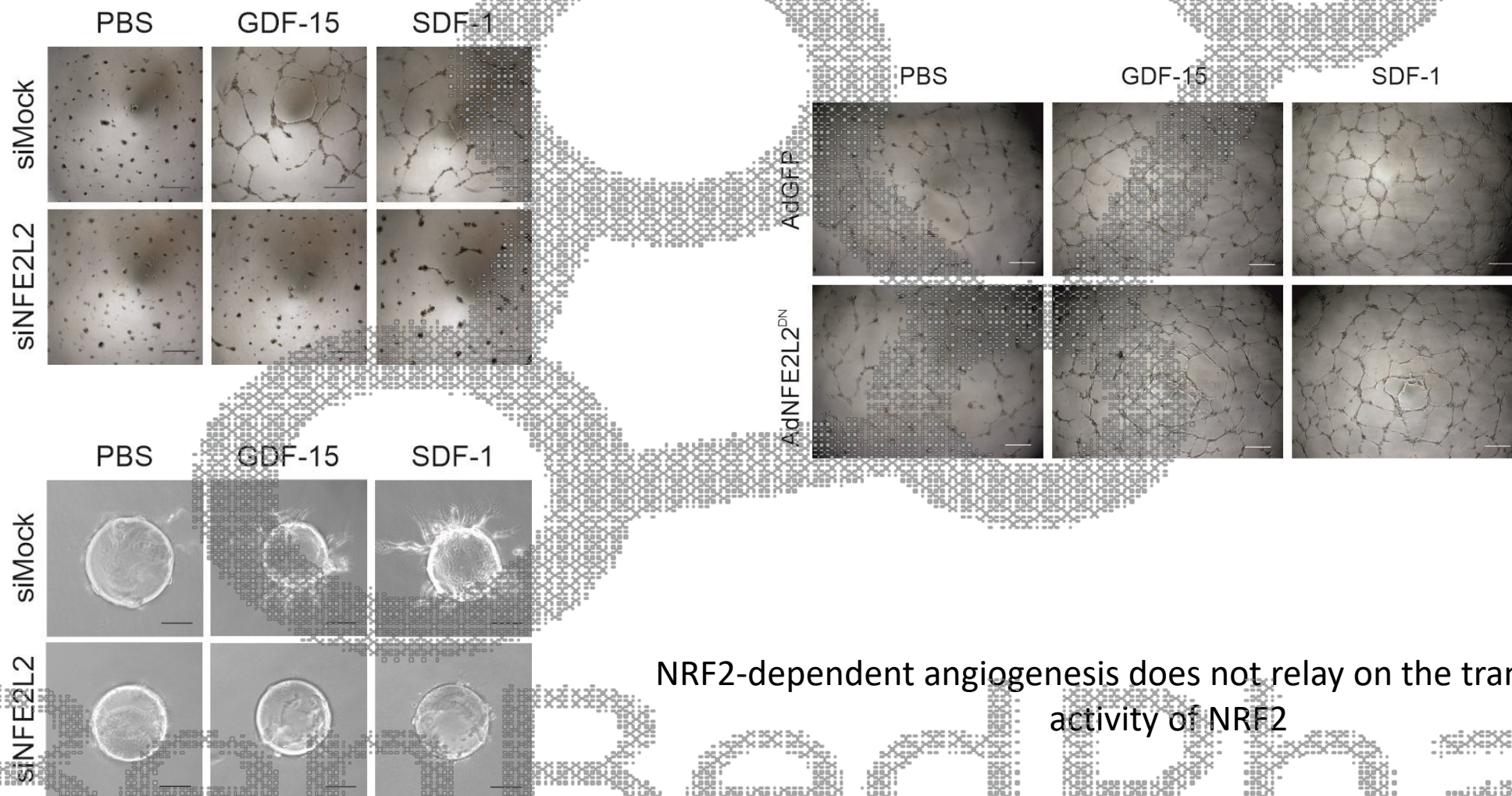
WT

tKO



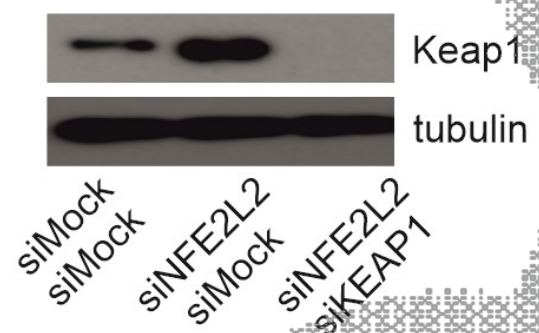
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NRF2-dependent angiogenesis

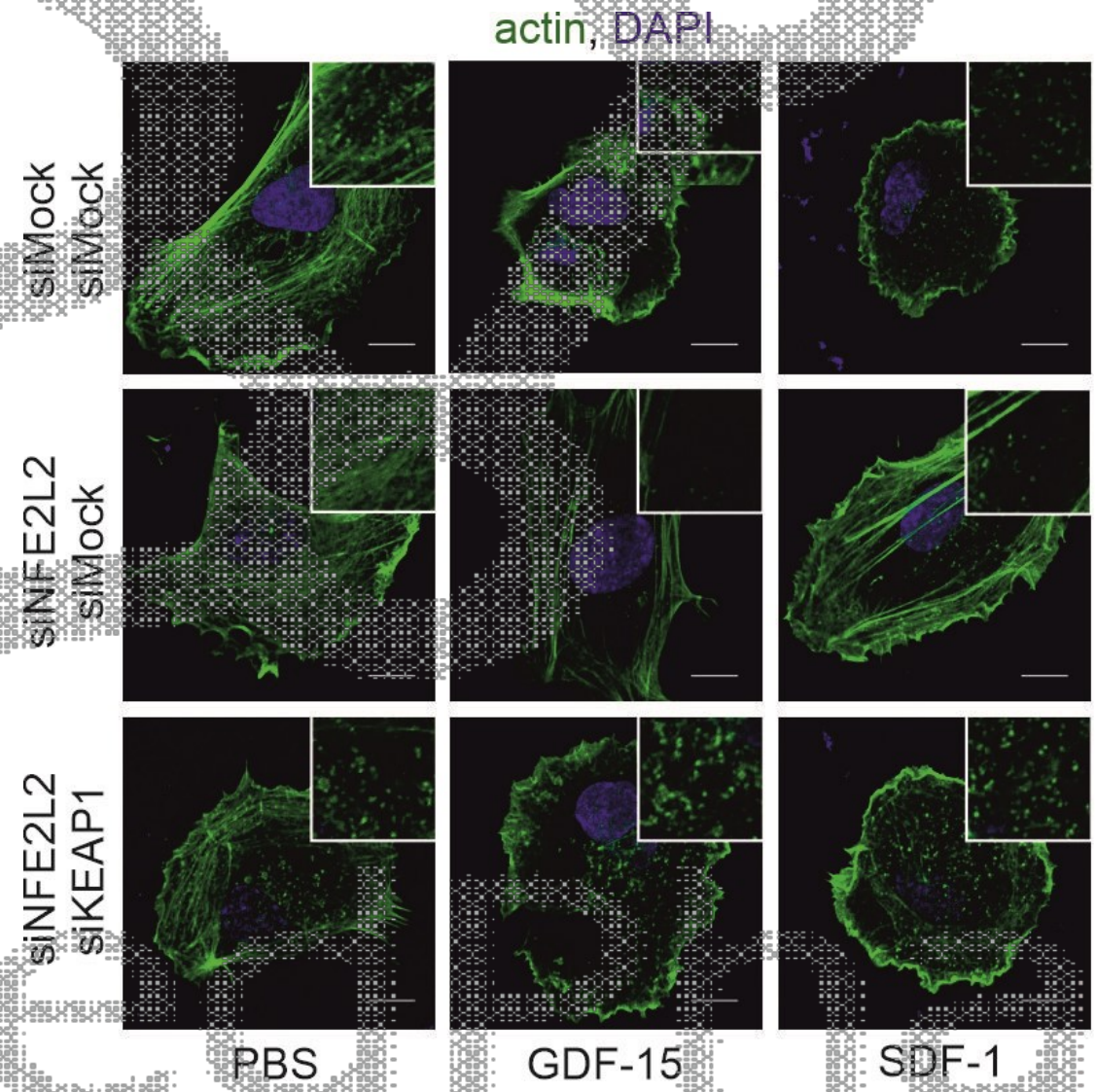


NRF2-dependent angiogenesis does not relay on the transcriptional activity of NRF2

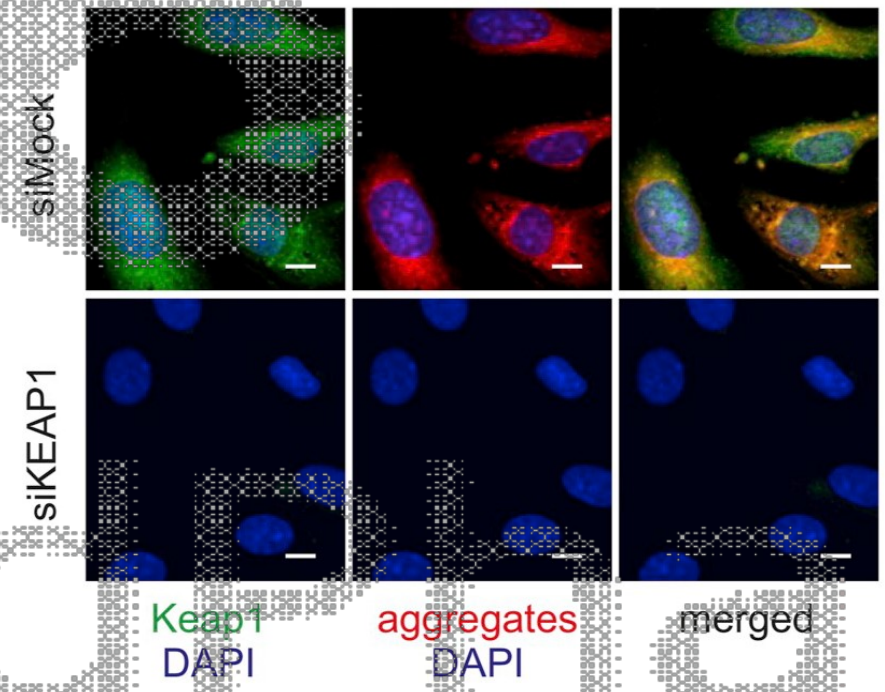
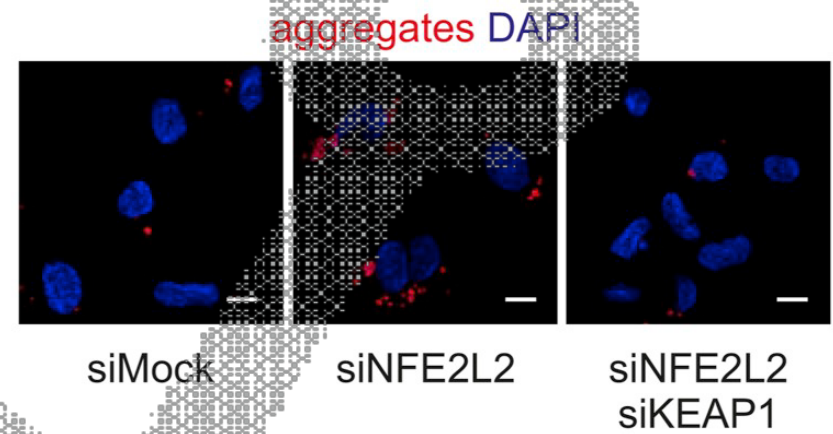
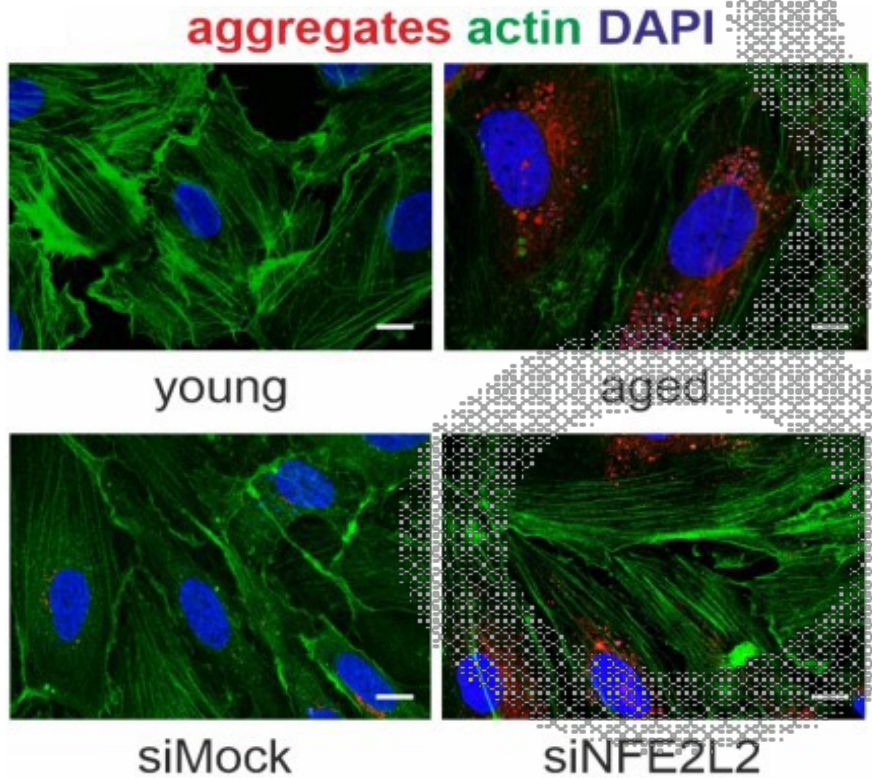
Unrestrained KEAP1 blocks angiogenesis



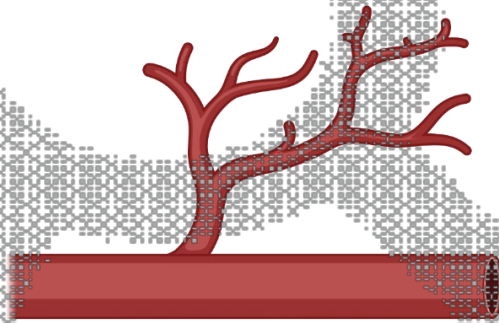
NRF2 keeps KEAP1 in check



Protein aggregation in EC



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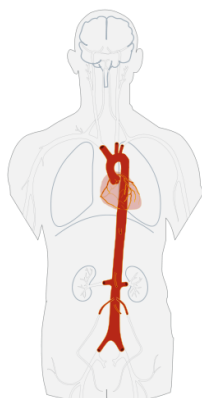


NRF2 deficiency improves blood flow restoration
(indirect effects) although it blocks angiogenic response of EC (direct effects)

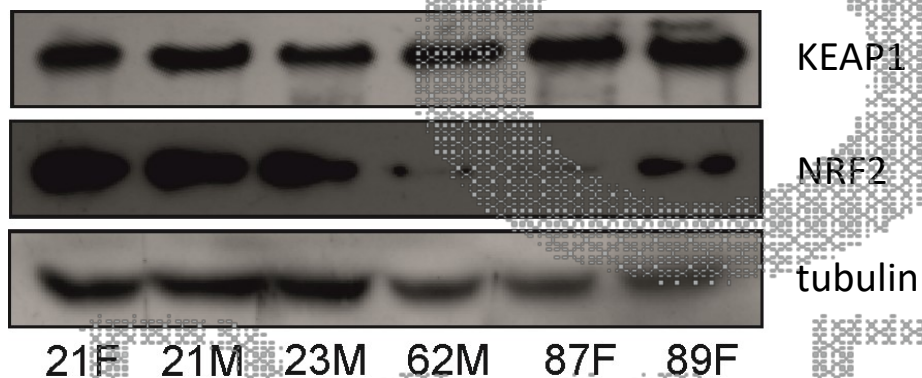
Postulated discriminating factor: inflammation and KEAP1

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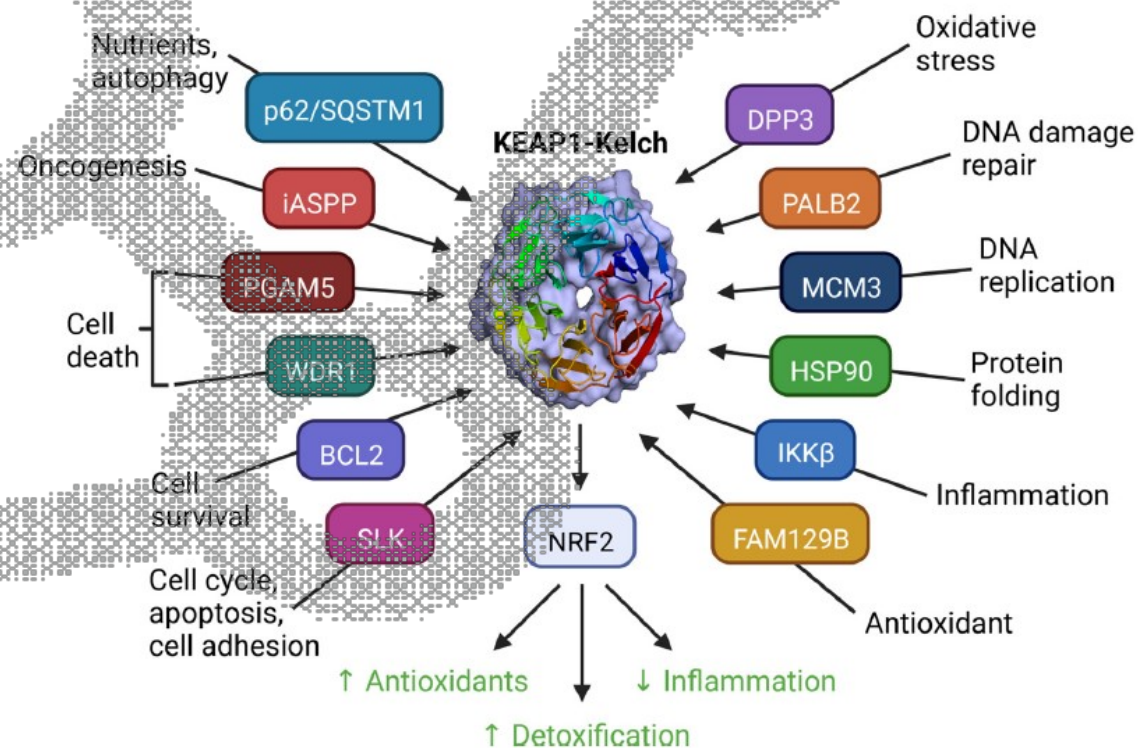
KEAP1 interactome and off-NRF2 effects



aortic ECs



S-nitrosation, proteostasis, mitochondria homeostasis, cytoskeleton regulation, and cell cycle progression



KEAP1

- A redox sensor
- NRF2 repressor
- A modulator of cytoskeleton, proteostasis, S-nitrosation, mitochondria homeostasis
- Broad interactome
- KEAP1 KD: reversal effect on senescence, angiogenesis impairment, loss of proteostasis





Thank you!

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