9th World Conference

The Future of Science - Secrets of Longevity

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Istituto Europeo di Oncologia

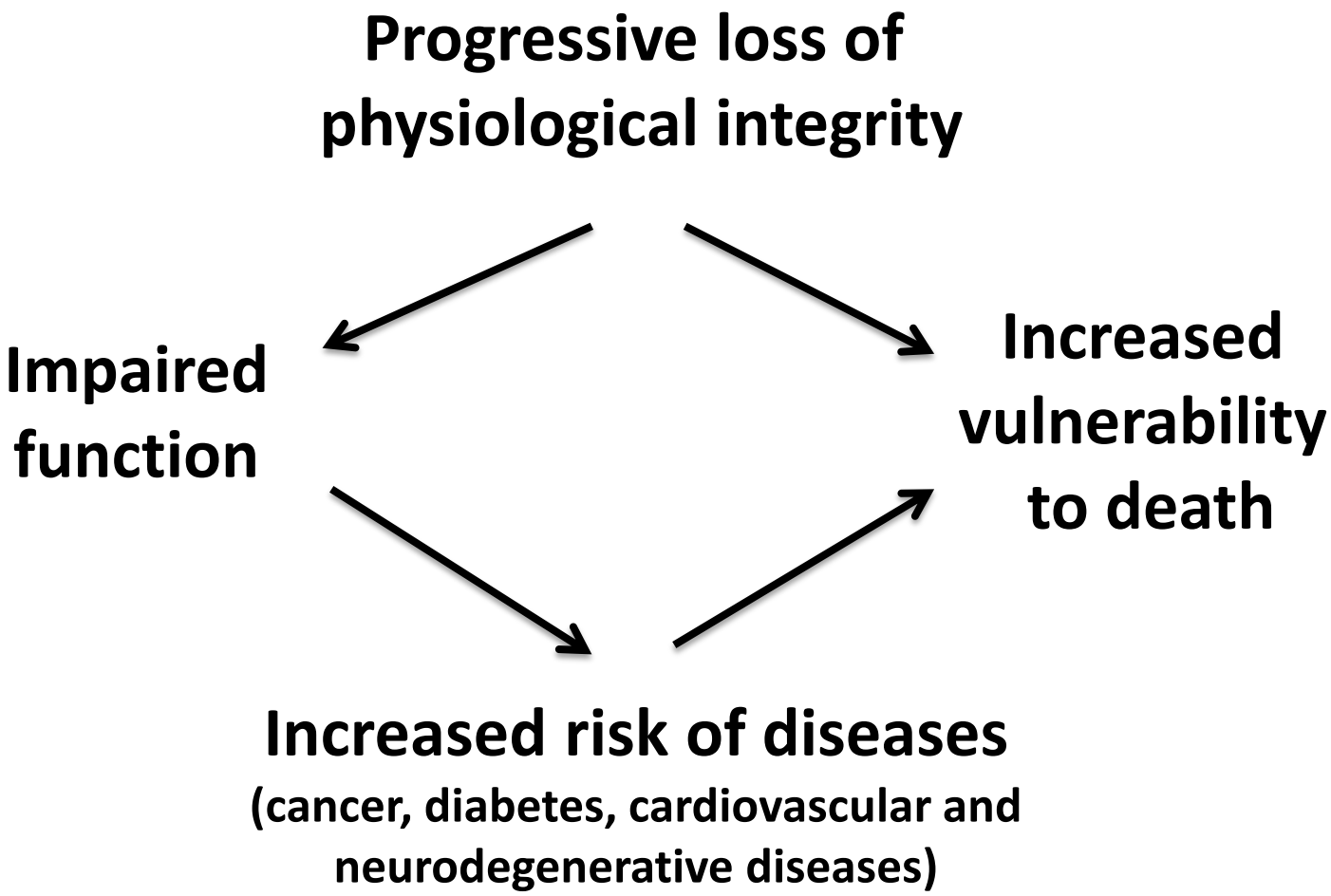
Aging

Progressive loss of physiological integrity

Impaired function

Increased vulnerability to death

Aging

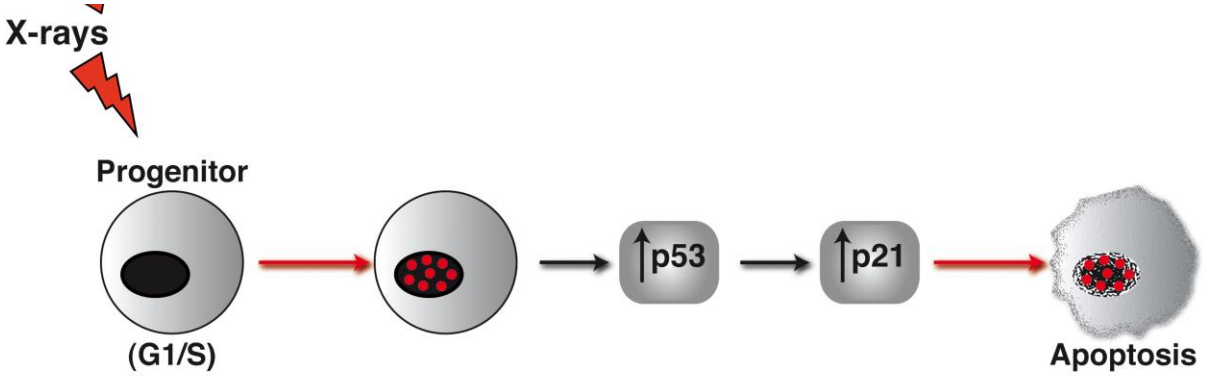

Progressive loss of physiological integrity
Impaired function
Increased vulnerability to death
Increased risk of diseases
(cancer, diabetes, cardiovascular and neurodegenerative diseases)

Aging

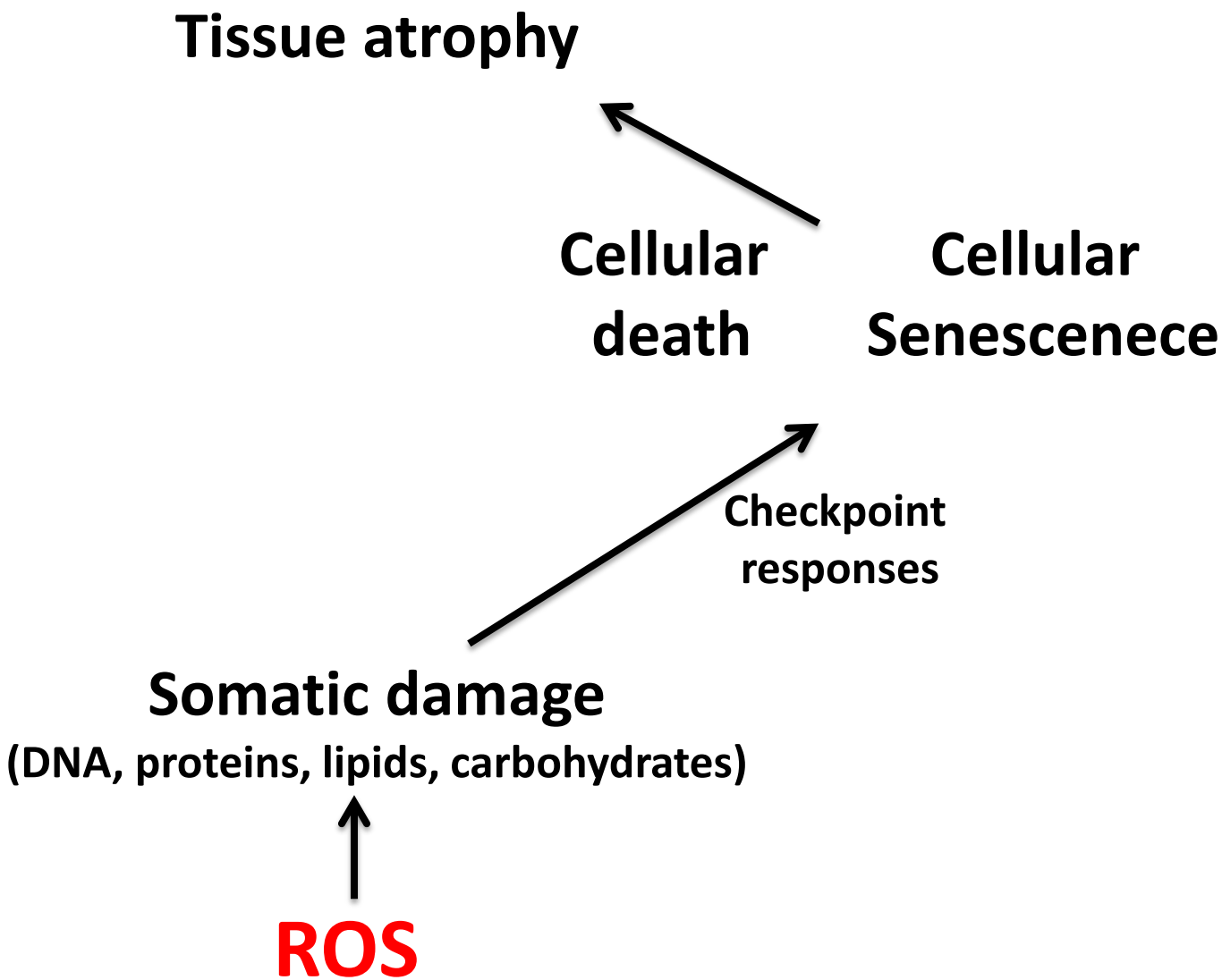
Tissue atrophy

Somatic damage
(DNA, proteins, lipids, carbohydrates)

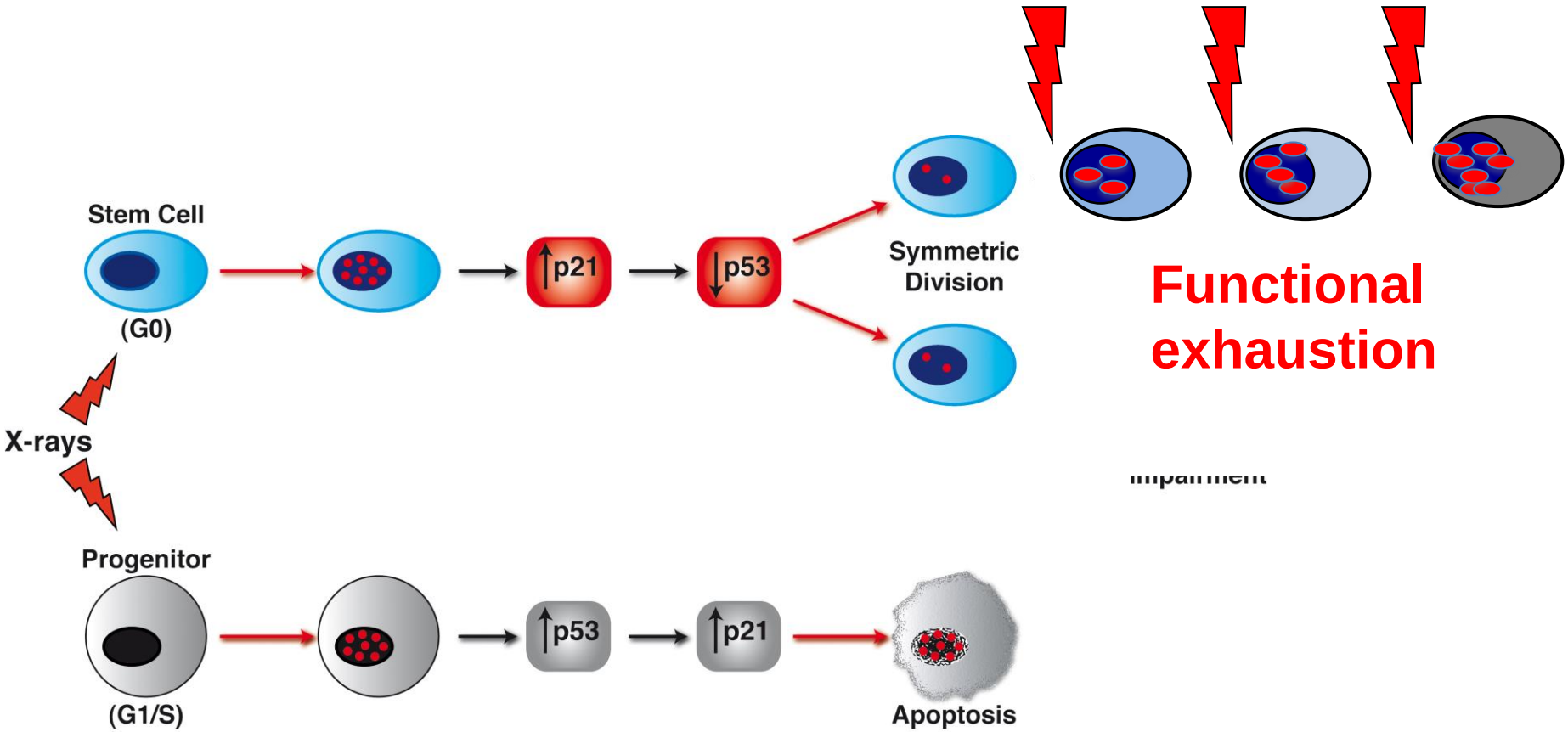
Cells have evolved cellular responses to DNA-damage that leads to loss of proliferative potential or death



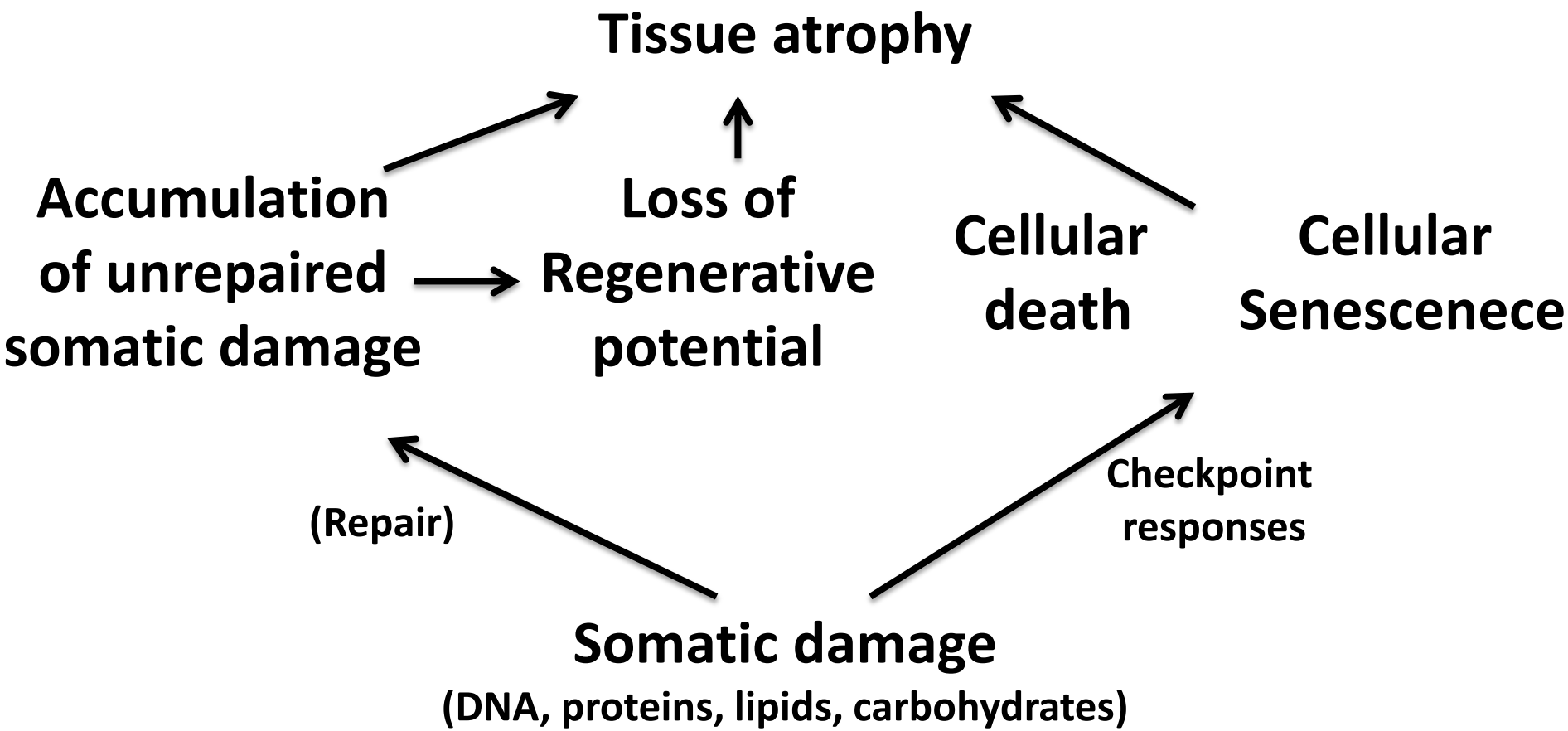
Aging


Tissue atrophy
Cellular death
Cellular Senescenece
Checkpoint responses
Somatic damage
(DNA, proteins, lipids, carbohydrates)
ROS

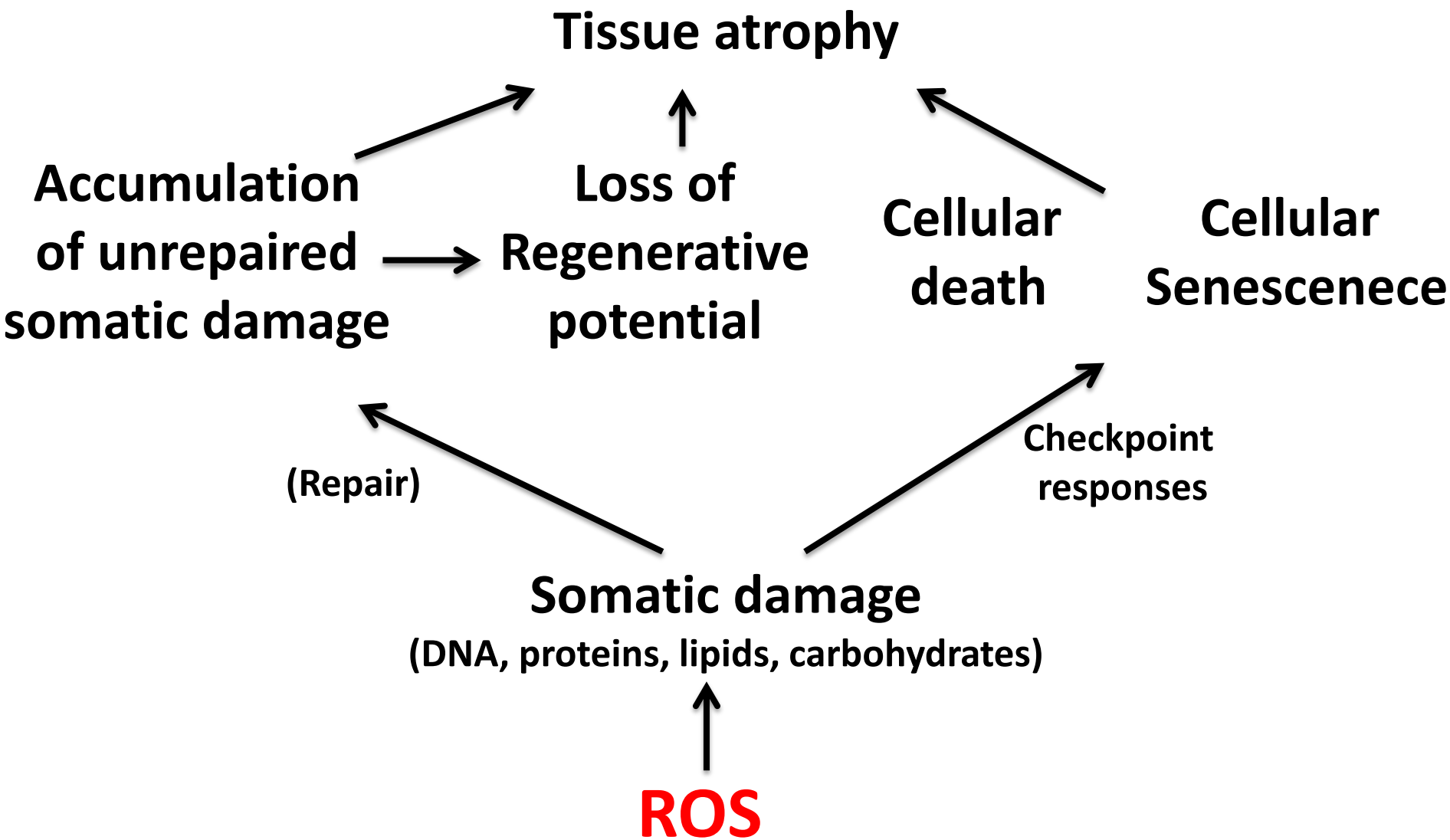
Stem cells have evolved unique responses to DNA-damage that leads to their immediate expansion and limits their regenerative potential



Aging


Tissue atrophy
Accumulation of unrepaired somatic damage
Loss of Regenerative potential
Cellular death
Cellular Senescenece
(Repair)
Checkpoint responses
Somatic damage
(DNA, proteins, lipids, carbohydrates)

Aging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Accumulation of unrepaired somatic damage
Loss of Regenerative potential
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(Repair)
Checkpoint responses
Somatic damage
(DNA, proteins, lipids, carbohydrates)
ROS

Aging:
Is it influenced by *environmental* or *genetic* factors?

Environment:

- **Demographic and twin studies: environment is much more important determinant of human ageing**
- **Caloric restriction extends life span**

Calorie Restriction (CR)

(Reduction of dietary calorie intake, w/o malnutrition)

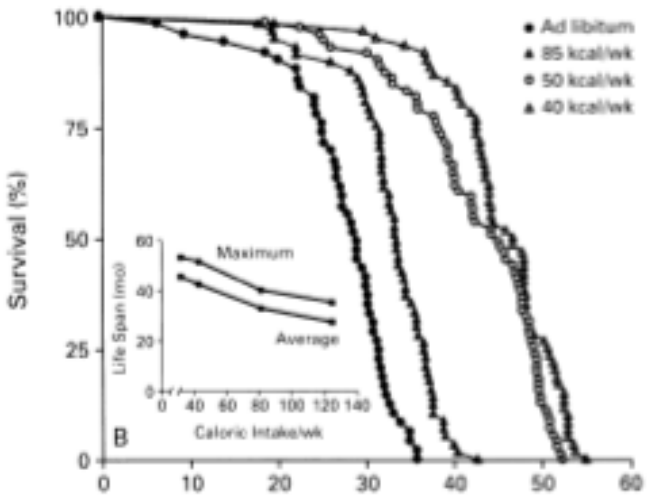
is the most robust and reproducible treatment-modality known to slow aging and extend life span

Species	Life-span Increase
Cerevisiae	75%
C. elegans	46%
D. melanogaster	28%
Medflies	22%
Grasshoppers	40%
Spiders	212%
Water fleas	69%
Rotifers	60%
Hamsters	30%
Mice	65%
Rats	85%
Dogs	16%

The effects of Calorie Restriction have been documented in diverse species, from single-celled organisms to mammals

Effects of Calorie Restriction in mice

Extends both average and maximal life span



Decreases the incidence of age-related diseases (cancer, cardiovascular diseases, brain diseases)

Aging:
Is it influenced by *environmental* or *genetic* factors?

Environment:

- **Demographic and twin studies: environment is much more important determinant of human ageing**
- **Caloric restriction extends life span**

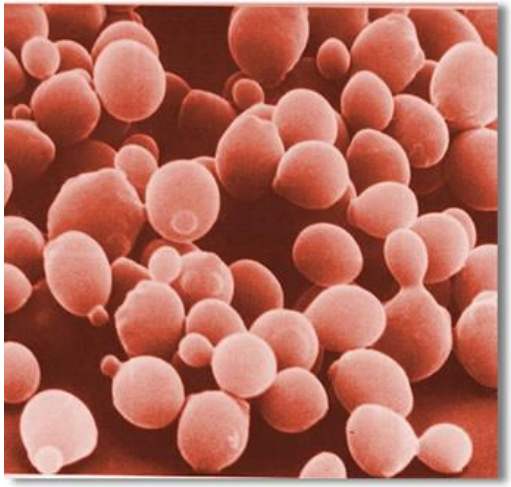
Genes:

- **Different species exhibit different life span**

1980s: mutations in single genes can significantly extend lifespan in *Caenorhabditis elegans*

Longevity Mutations

1980-2013: Hundreds of longevity mutations have been identified in model organisms (yeasts, nematodes, fruit flies, mice)

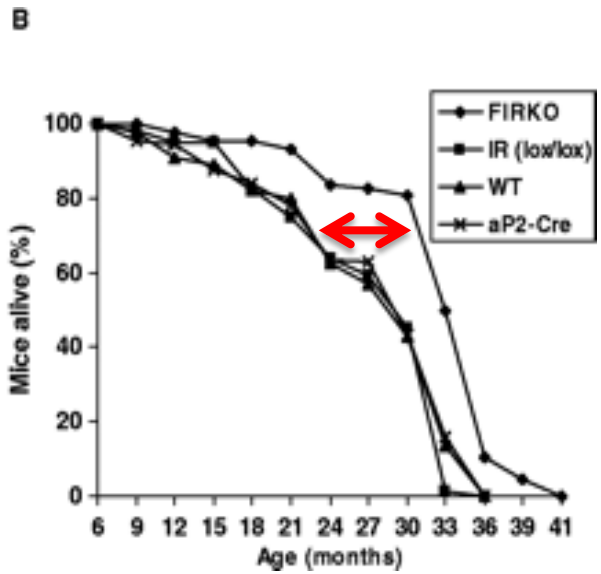


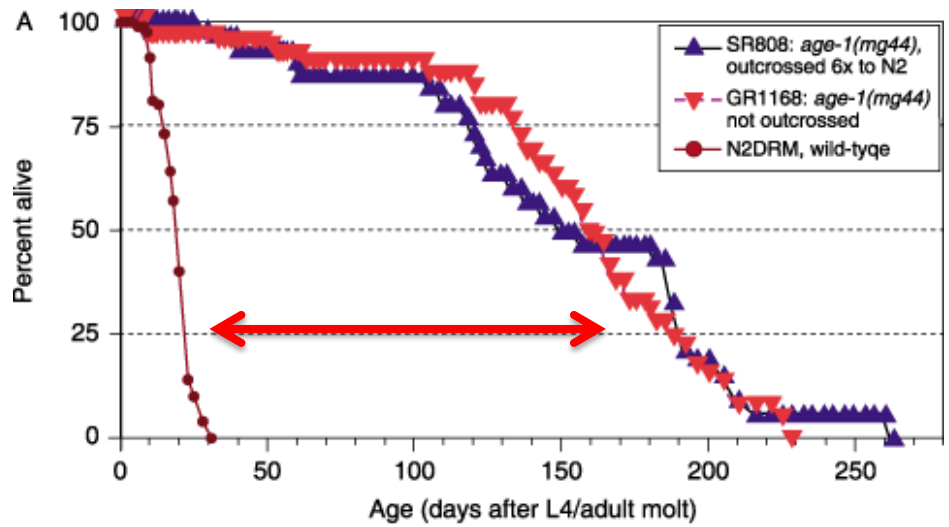
- ✓ Mutations that inactivate or decrease gene function (aging genes)
- ✓ Mutations that activate gene function (longevity genes)

~25 Aging-genes in mice

GENE	PHENOTYPE	REFERENCES
Brca1 + p53	Premature ageing	Cao et al., 2003
Bub3 + Rae1	Premature ageing	Baker et al., 2006
BubR1 BUB1B	Premature aging	Baker et al., 2004
C/EBPCCAAT/enhancer-binding protein	20% increase in lifespan	Chiu et al., 2004
GH growth hormone	Putative accelerated ageing	Bartke, 2003
CSA	Possible premature ageing	Henning et al., 1995
GHR/BPgrowth hormone receptor	Increase in lifespan of 40-50%	Cochigano et al., 2000
klotho	Putative accelerated ageing	Kuro-o et al., 1997
Ku86, XRCC5	Premature aging	Vogel et al., 1999
LMNA Hutchinson-Gilford syndrome	Possible premature ageing	Eriksson et al., 2003
MsrA	Decreased lifespan	Moskovitz et al., 2001
P53	Premature ageing	Tyner et al., 2002
P63, TP73L	Signs of premature ageing	Keyes et al., 2005
P66shc	Retarded ageing	Migliaccio et al., 1999
PASG	Premature ageing	Sun et al., 2004
Pit1 Snell dwarf mouse	Lifespan increase of 42%	Flurkey et al., 2001
PolgA	Possible premature ageing	Trifunovic et al., 2004
Prop1 Ames dwarf mouse	Over 50% increases in lifespan	Brown-Borg et al., 1996
SIRT6	Premature ageing	Mostoslavsky et al., 2006
Terc + Atm	Premature ageing	Wong et al., 2003
Terc + WRN Werner syndrome	Premature ageing	Chang et al., 2004
uPA	20% increase in lifespan	Miskin and Masos, 1997
WRN	Possible accelerated ageing	Yu et al., 1996
XPD	Symptoms of premature ageing	De Boer et al., 2002

Their effect on life span is variable

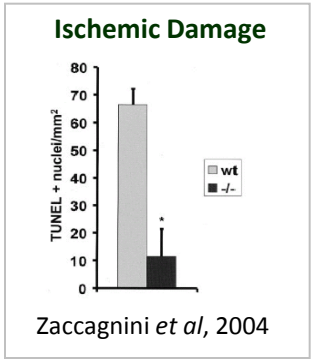




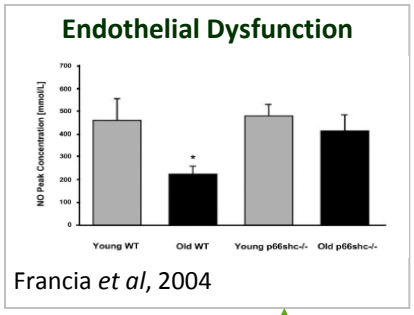
Mice:
20% increased lifespan

Nematodes:
10-fold increased lifespan

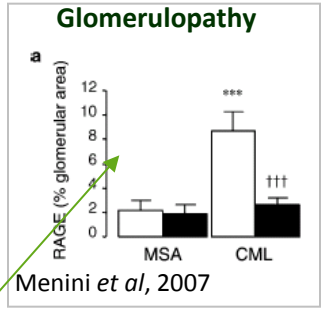
Most longevity-mutations reduce incidence/severity of late-onset diseases



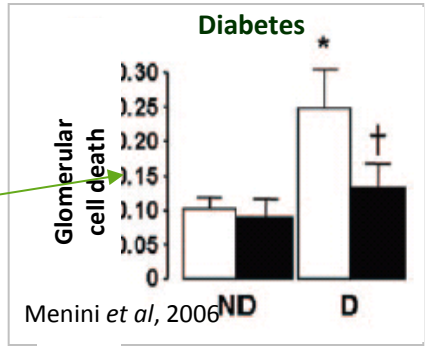
Zaccagnini *et al*, 2004



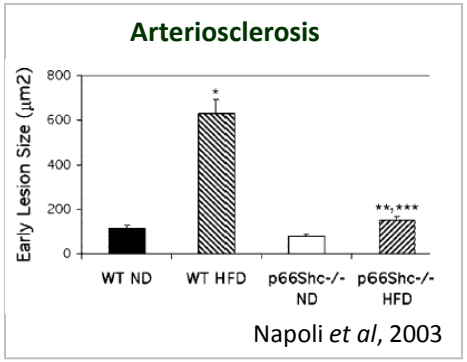
Francia *et al*, 2004



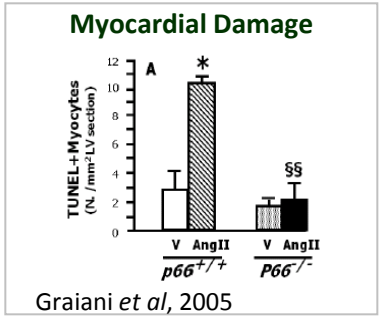
Menini *et al*, 2007



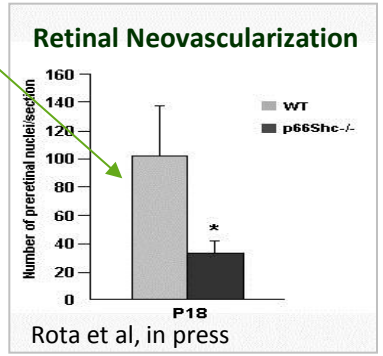
Menini *et al*, 2006



Napoli *et al*, 2003

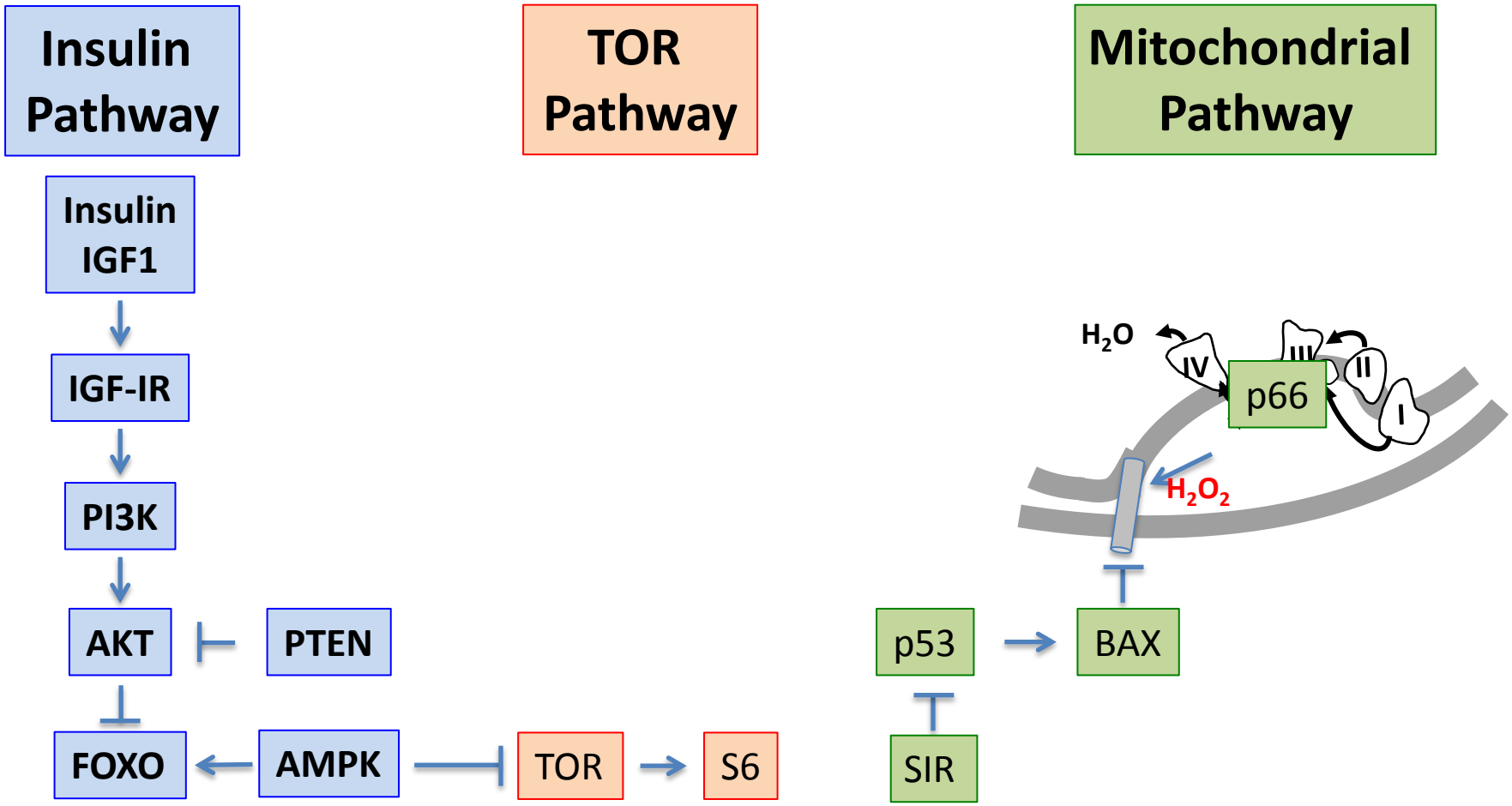


Graiani *et al*, 2005

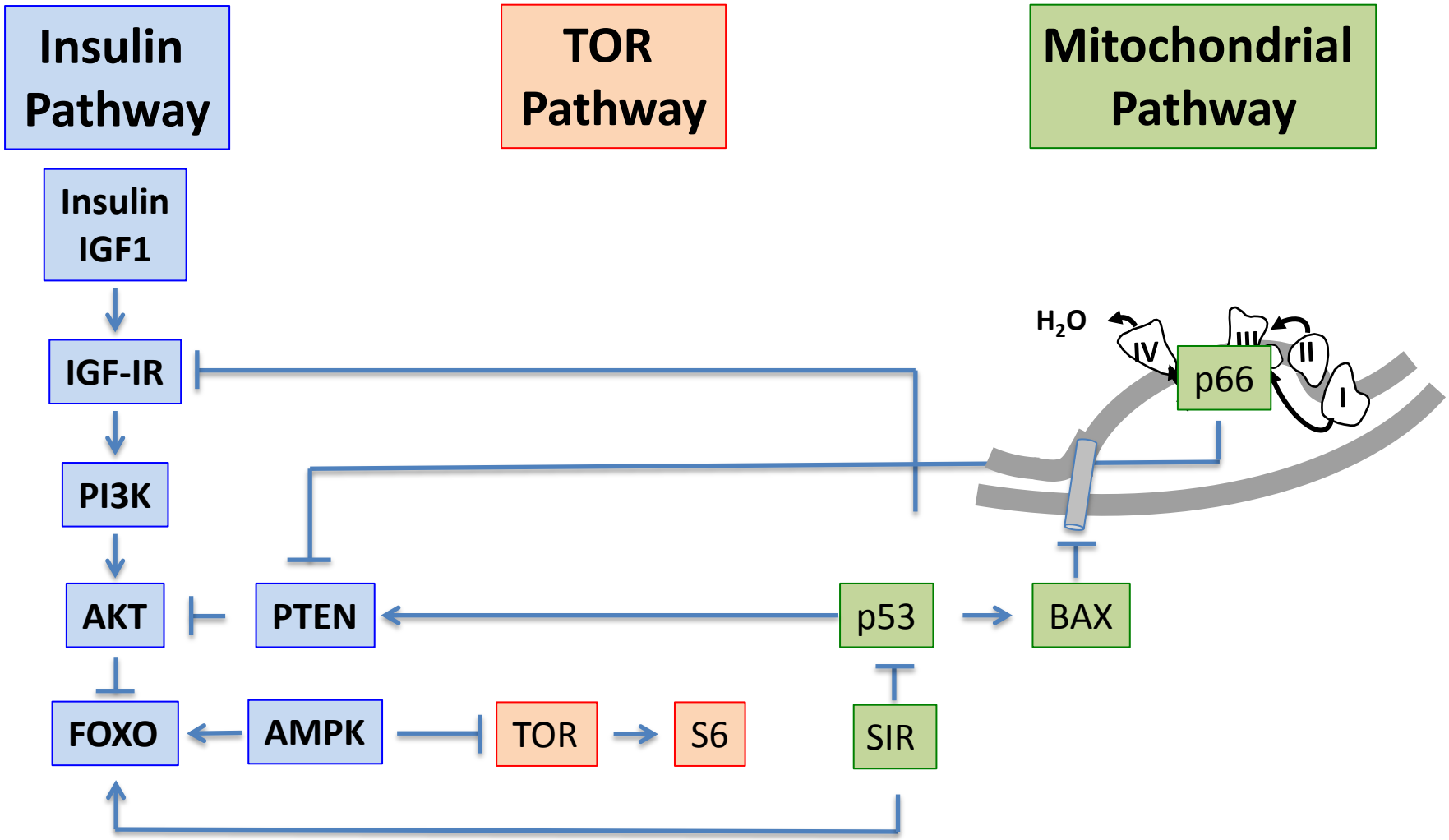


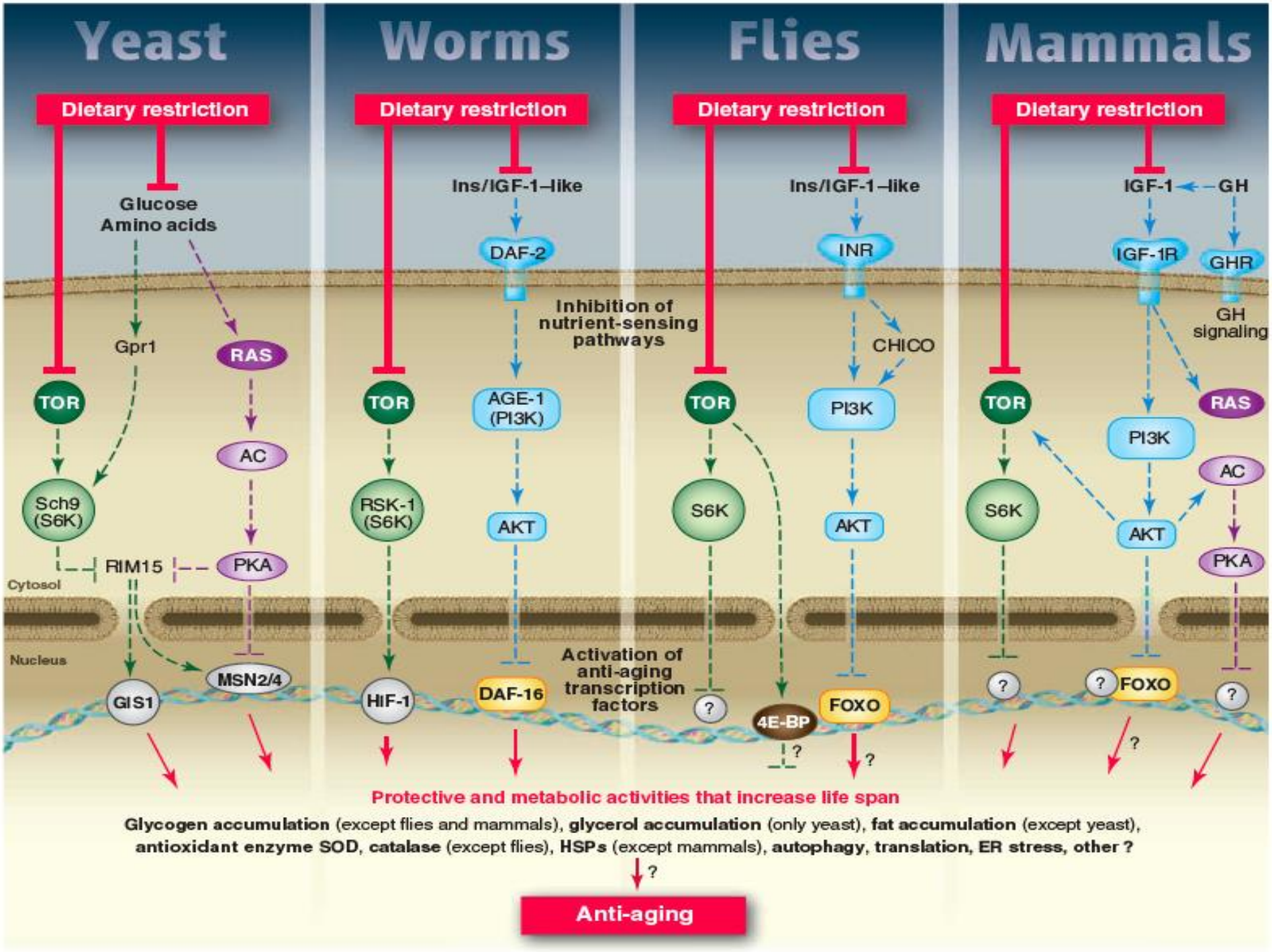
Rota et al, in press

Most longevity genes act in evolutionarily conserved pathways that regulate growth, energy metabolism, and/or reproduction



These pathways are inter-connected and are involved in nutrition sensing (Glucose, Aminoacids, Calories)




Yeast
Worms
Flies
Mammals
Dietary restriction
Dietary restriction
Dietary restriction
Dietary restriction
Glucose
Amino acids
Gpr1
RAS
TOR
AC
Sch9
(S6K)
RIM15
PKA
Cytosol
Nucleus
MSN2/4
GIS1
Ins/IGF-1–like
DAF-2
Inhibition of
nutrient-sensing
pathways
TOR
AGE-1
(PI3K)
RSK-1
(S6K)
AKT
HIF-1
DAF-16
Ins/IGF-1–like
INR
CHICO
TOR
PI3K
S6K
AKT
4E-BP
FOXO
Activation of
anti-aging
transcription
factors
IGF-1
GH
IGF-1R
GHR
GH
signaling
TOR
RAS
PI3K
AC
S6K
AKT
PKA
FOXO
Protective and metabolic activities that increase life span
Glycogen accumulation (except flies and mammals), glycerol accumulation (only yeast), fat accumulation (except yeast),
antioxidant enzyme SOD, catalase (except flies), HSPs (except mammals), autophagy, translation, ER stress, other ?
Anti-aging

- **Is programmed aging the physiological function of these genes?**

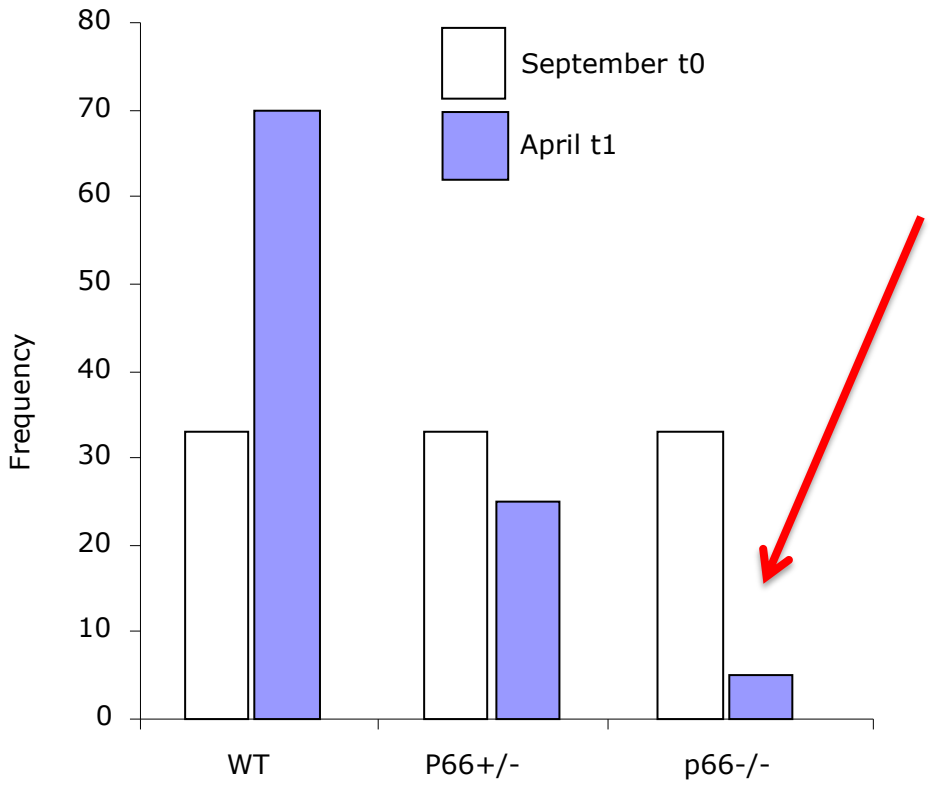
- **How/Why food/energy sensing and life-span regulation are connected?**

Our mice live in a protected environment

Do aging-genes increase early-life fitness in the wild?

Analysis of the life span of p66 mice under outdoor conditions (food competition; exposure to winter temperatures)

Wild condition selects against mutation of the p66 aging-gene



The health impact of mutating a aging gene might depend on environmental factors

Potected Environment

longer **lifespan**

Natural Environment

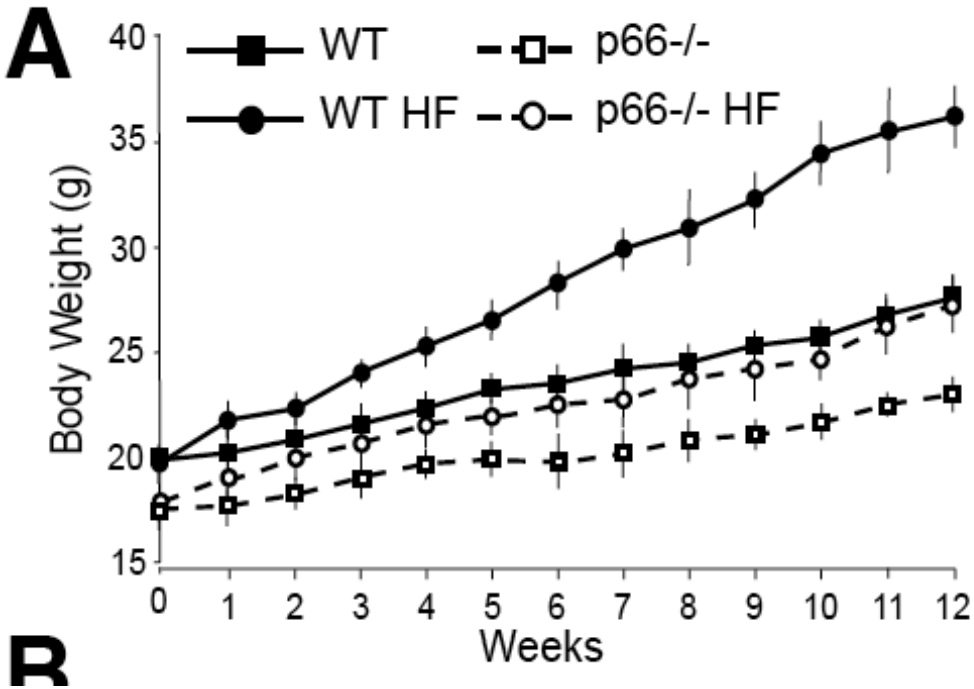
shorter **lifespan**

Why mice with mutation of the p66-aging gene do not survive in a natural environment?

- **No behavioral abnormalities or infection vulnerability**

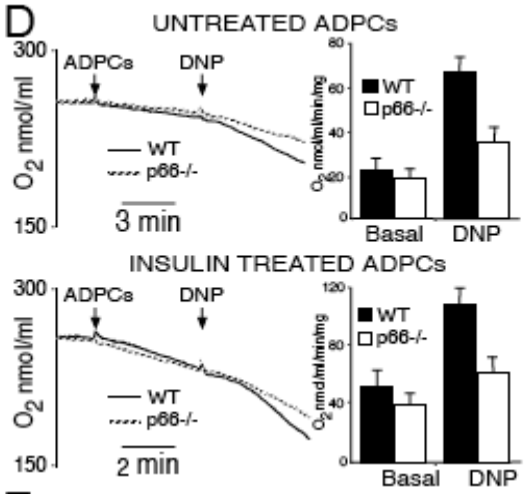
Why mice with mutation of the p66-aging gene do not survive in a natural environment?

- No behavioral abnormalities or infection vulnerability
- **Defective fat accumulation**

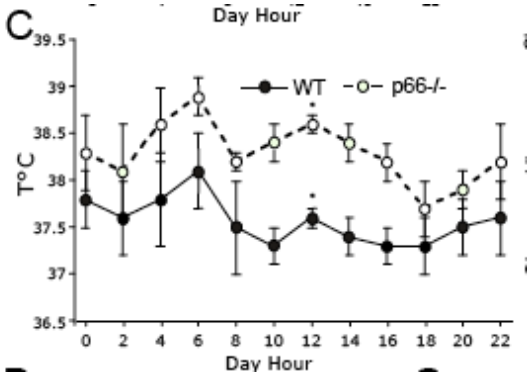


Why mice with mutation of the p66-aging gene do not survive in a natural environment?

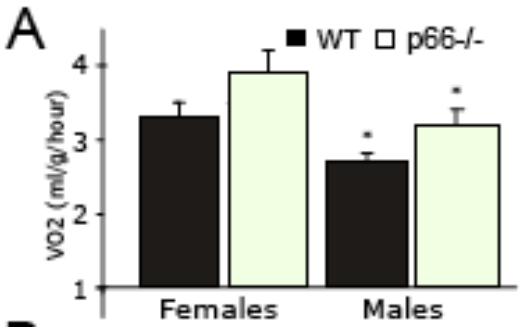
- No behavioral abnormalities or infection vulnerability
- Defective fat accumulation
- **Defective energy conservation**



Better mitochondrial coupling



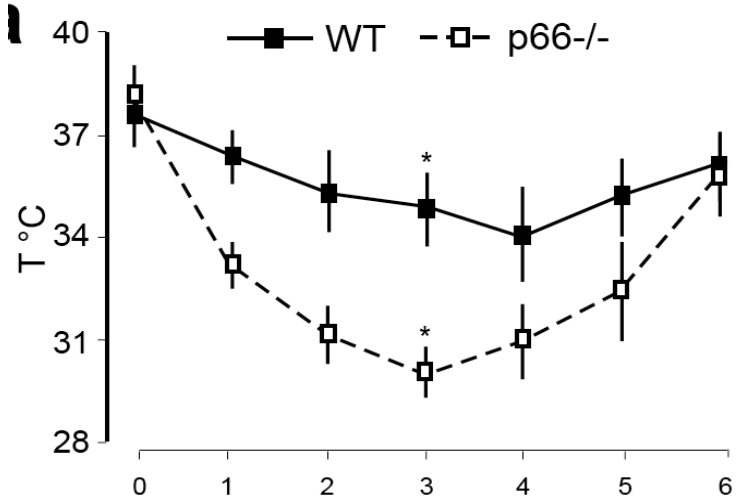
Increased basal body temperature



Higher energetic expenditure

Why mice with mutation of the p66-aging gene do not survive in a natural environment?

- No behavioral abnormalities or infection vulnerability
- Defective fat accumulation
- Defective energy conservation
- **Defective thermoregulation**



Why mice with mutation of the p66-aging gene do not survive in a natural environment?

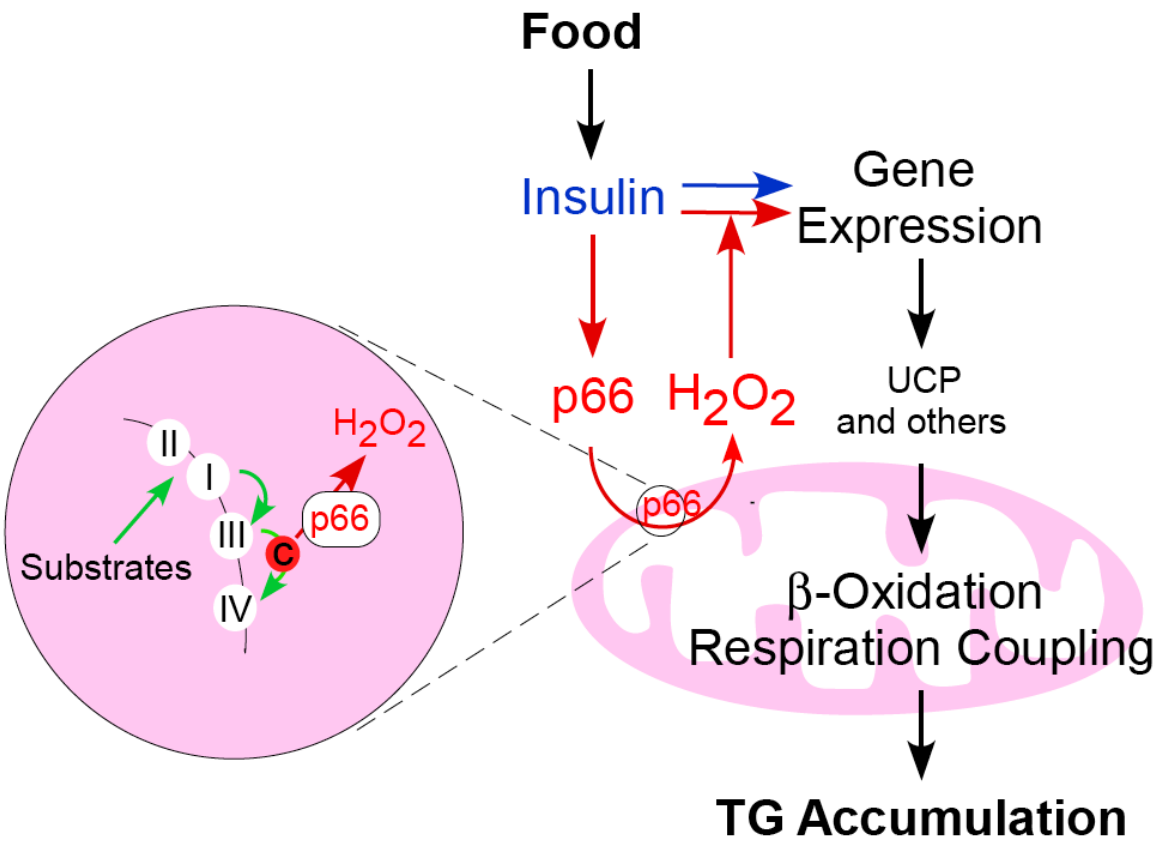
- No behavioral abnormalities or infection vulnerability
- Defective fat accumulation
- Defective energy conservation
- Defective thermoregulation
- **Defective reproduction**

P66-mutant mice are highly sensitive to low-temperatures and food-scarcity

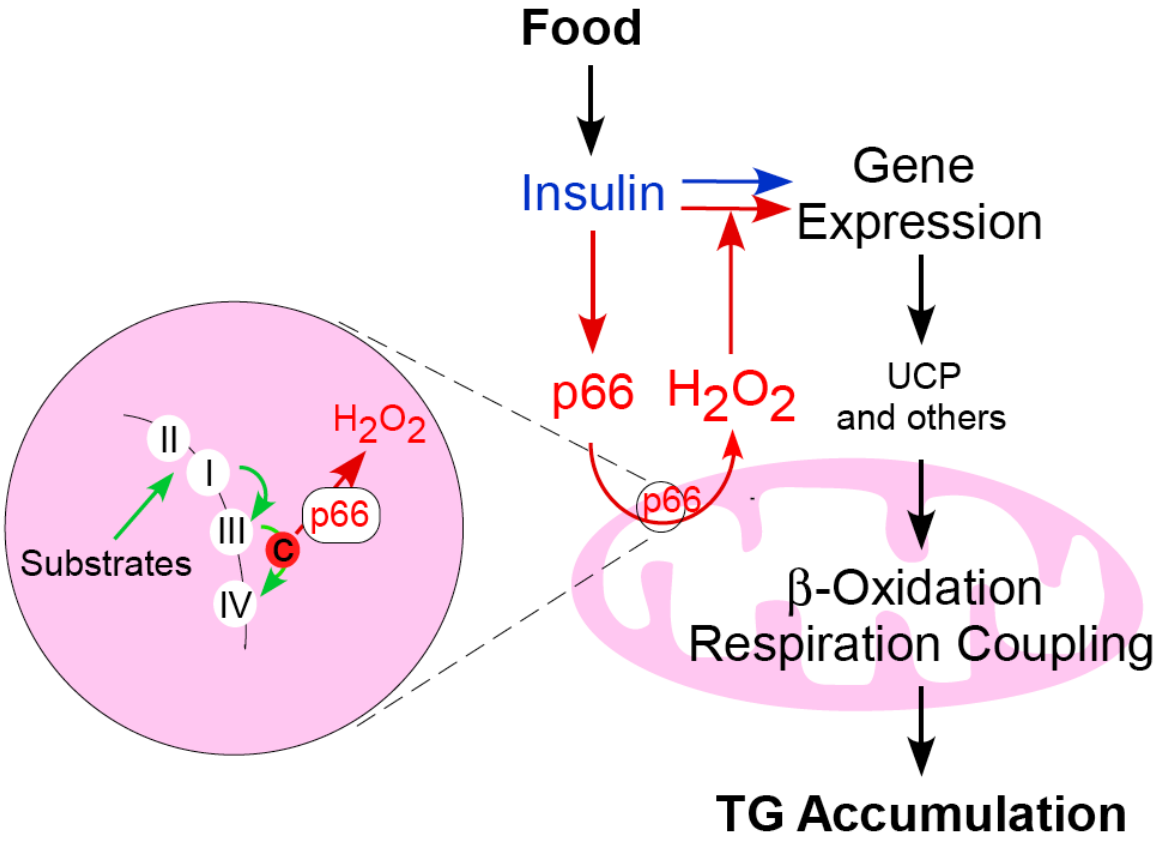
- No behavioral abnormalities or infection vulnerability
- Defective fat accumulation
- Defective energy conservation
- Defective thermoregulation
- Defective reproduction

50% mortality of p66 mice when simultaneously starved and exposed to cold

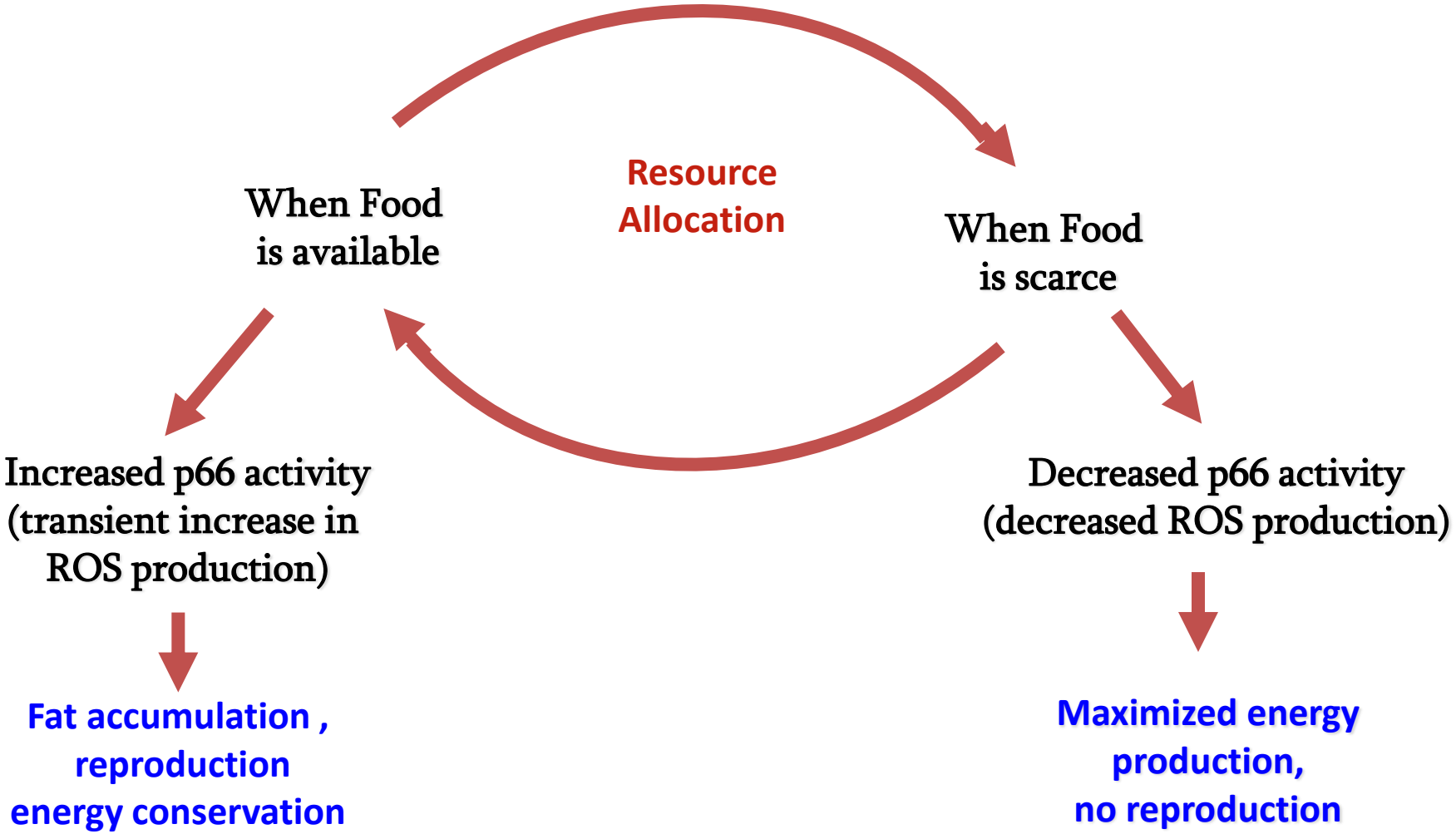
p66 senses the mitochondrial energetic state and regulates insulin signaling using H_2O_2 as second messenger



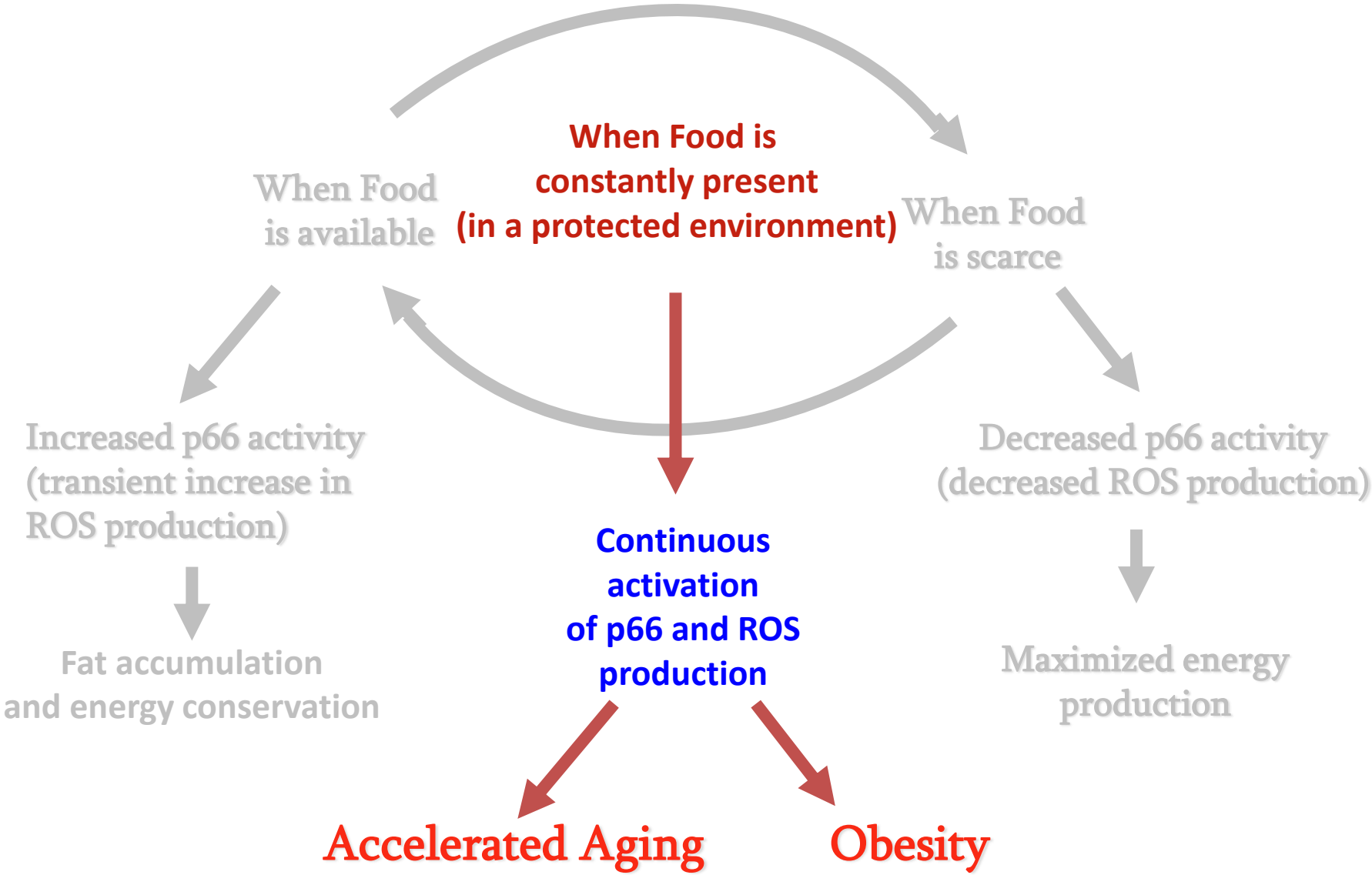
p66 is activated by energy intake (and repressed by starvation)



p66 regulates adaptation of the organism to changes in the energetic niche

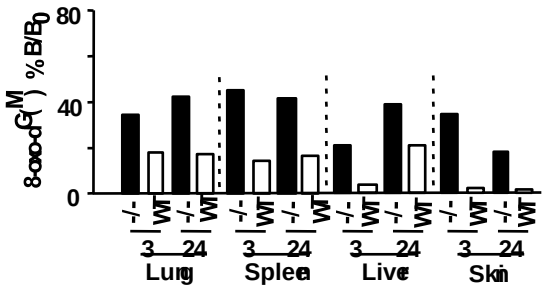


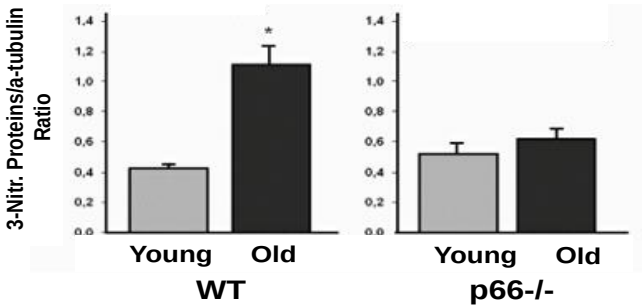
The function of p66 becomes "detrimental" when food is constantly present



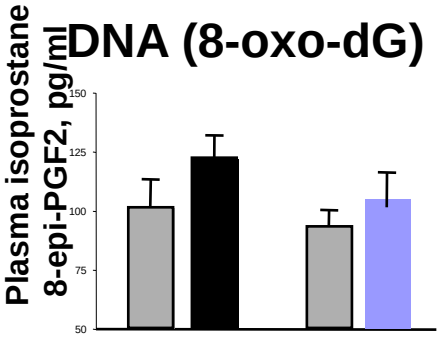
In a protected environment, p66 increases intracellular oxidative stress, accelerates aging and induces obesity

- **Increases oxidative stress**





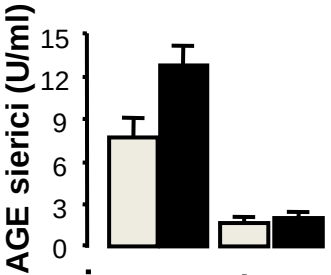
DNA (8-oxo-dG)



High Fat: - + - +

WT p66-/-

LIPIDS (SERUM ISOPROSTANE)



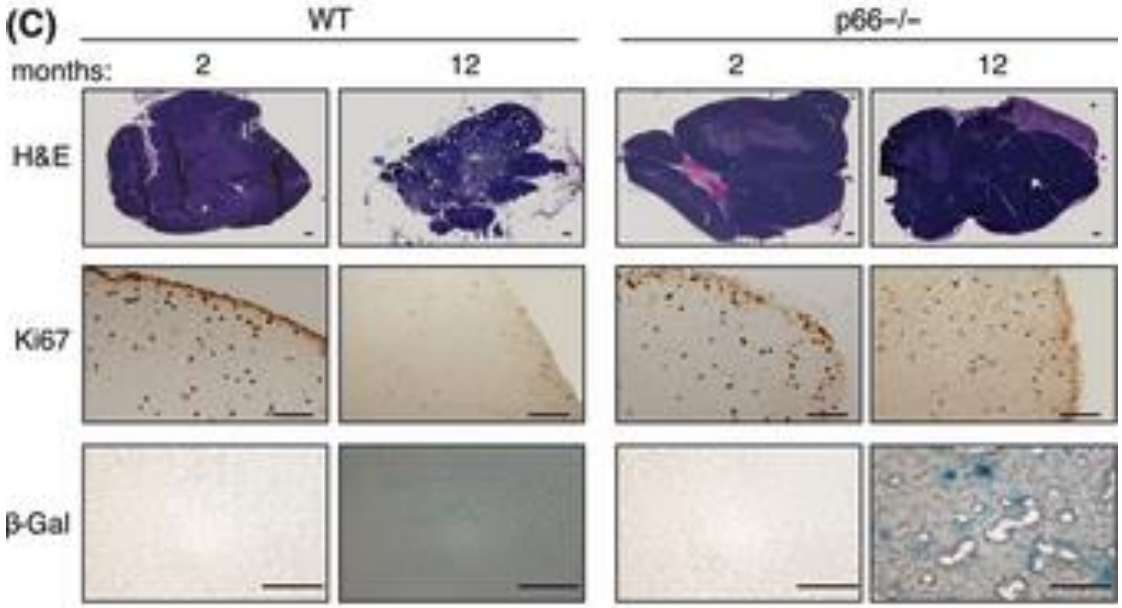
Hyperglycemia: - + - +

WT p66-/-

GLYCANS (SERUM AGE)

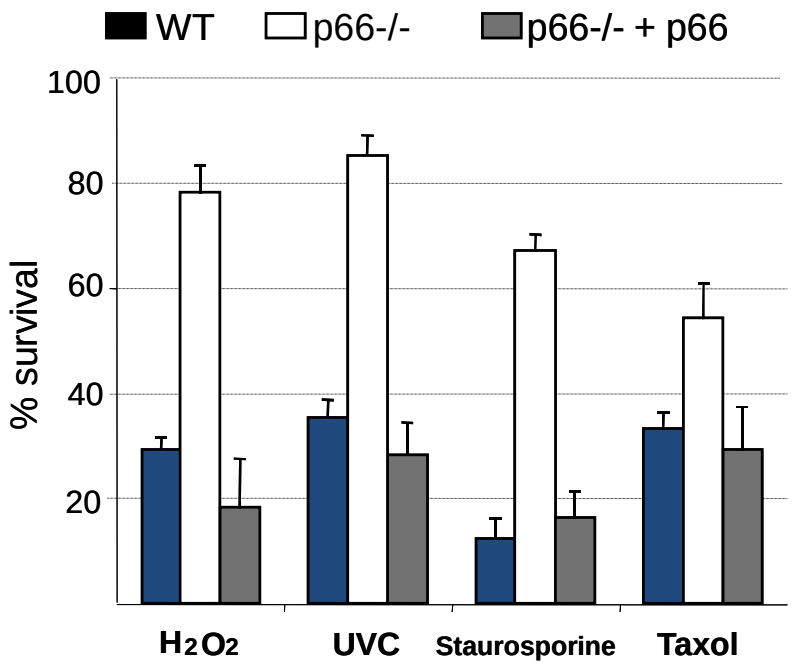
In a protected environment, p66 increases intracellular oxidative stress, accelerates aging and induces obesity

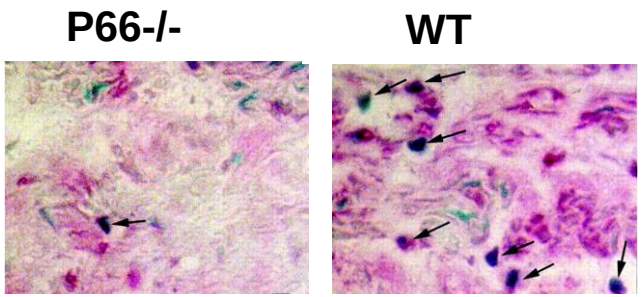
- Increases oxidative stress
- **induces cellular senescence**



In a protected environment, p66 increases intracellular oxidative stress, accelerates aging and induces obesity

- Increases oxidative stress
- induces cellular senescence
- **increases stress-induced apoptosis**

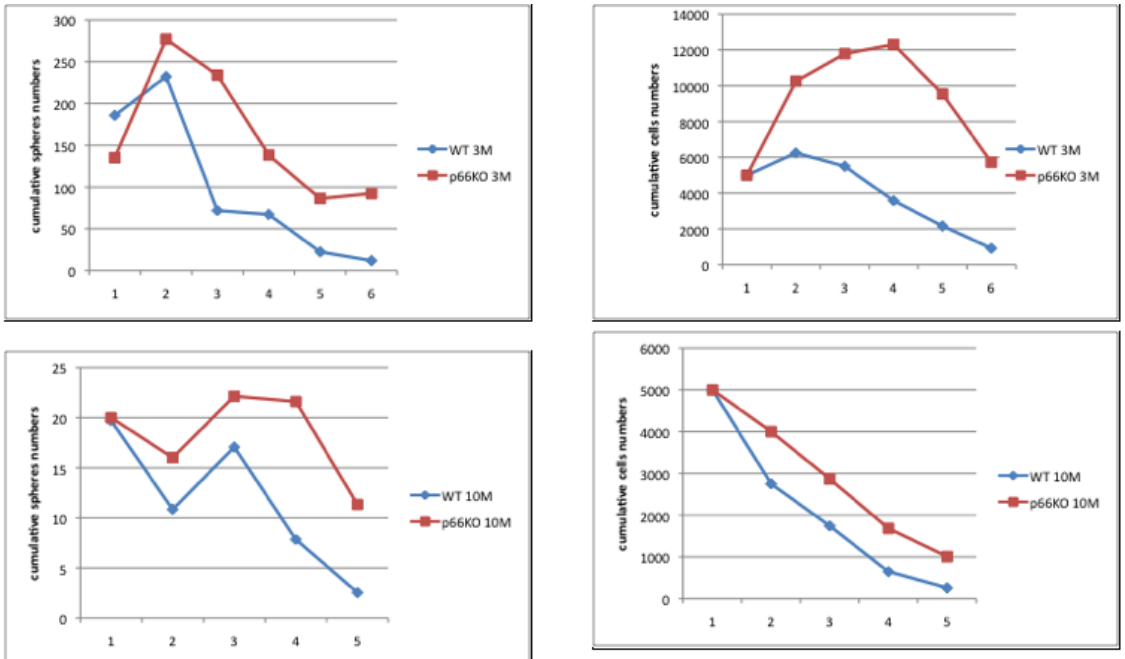




APOPTOTIC CELLS AFTER HYGH FAT DIET

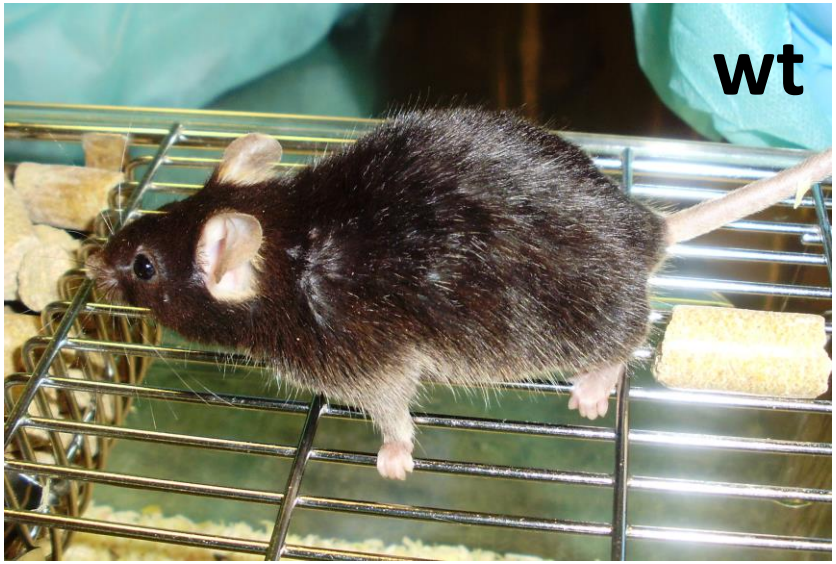
In a protected environment, p66 increases intracellular oxidative stress, accelerates aging and induces obesity

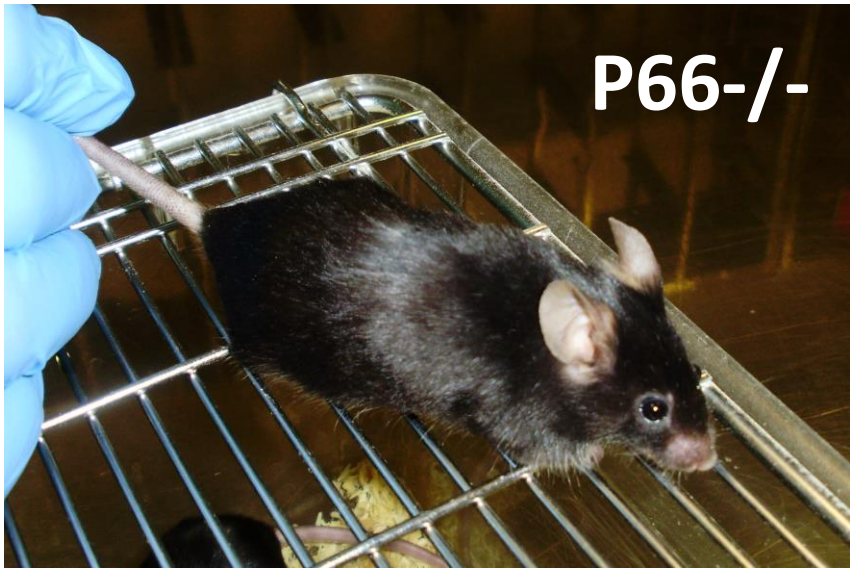
- Increases oxidative stress
- induces cellular senescence
- increases stress-induced apoptosis
- **reduces numbers of Stem Cells**



In a protected environment, p66 increases intracellular oxidative stress, accelerates aging and induces obesity

- Increases oxidative stress
- induces cellular senescence
- increases stress-induced apoptosis
- reduces numbers of Stem Cells
- **accelerates aging**





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- Increases oxidative stress
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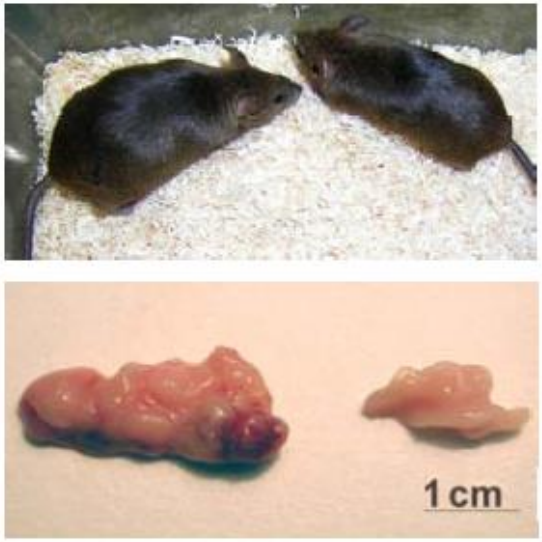
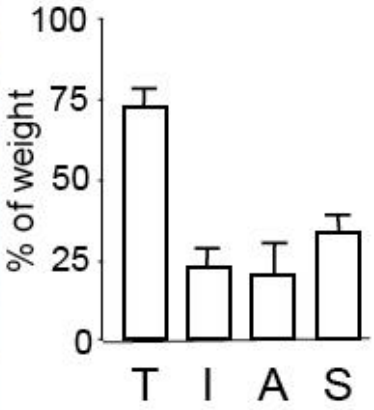
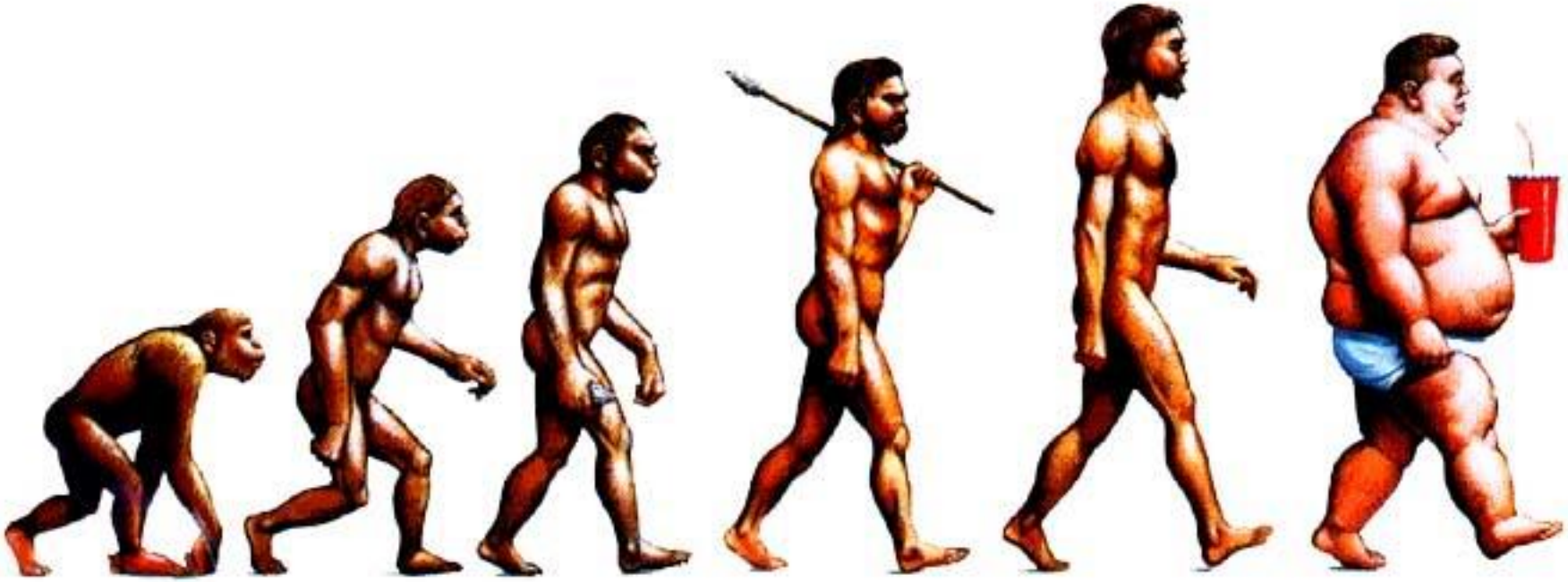
- reduces numbers of Stem Cells
- accelerates aging
- **induces obesity**

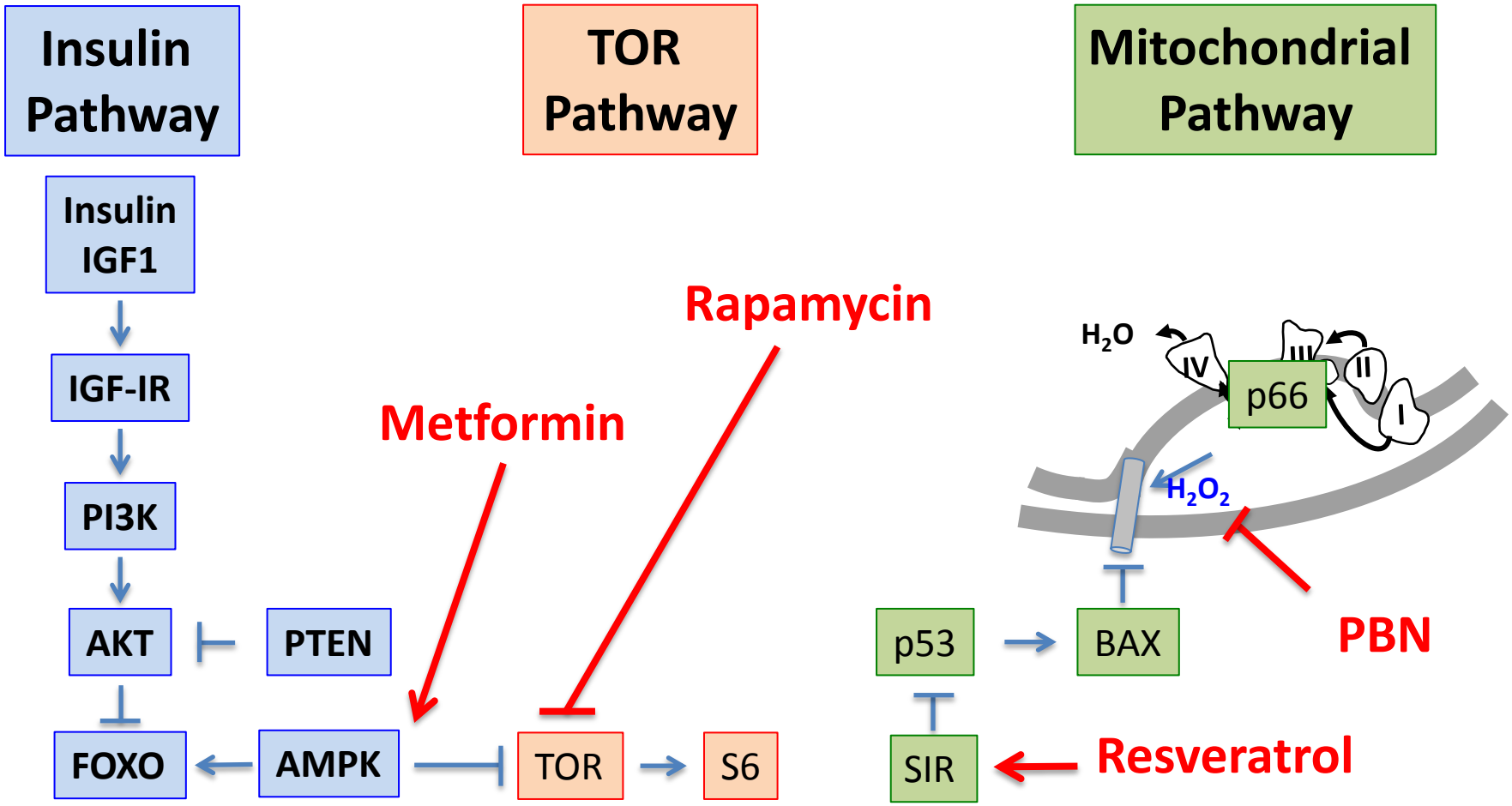


Inguinal fat

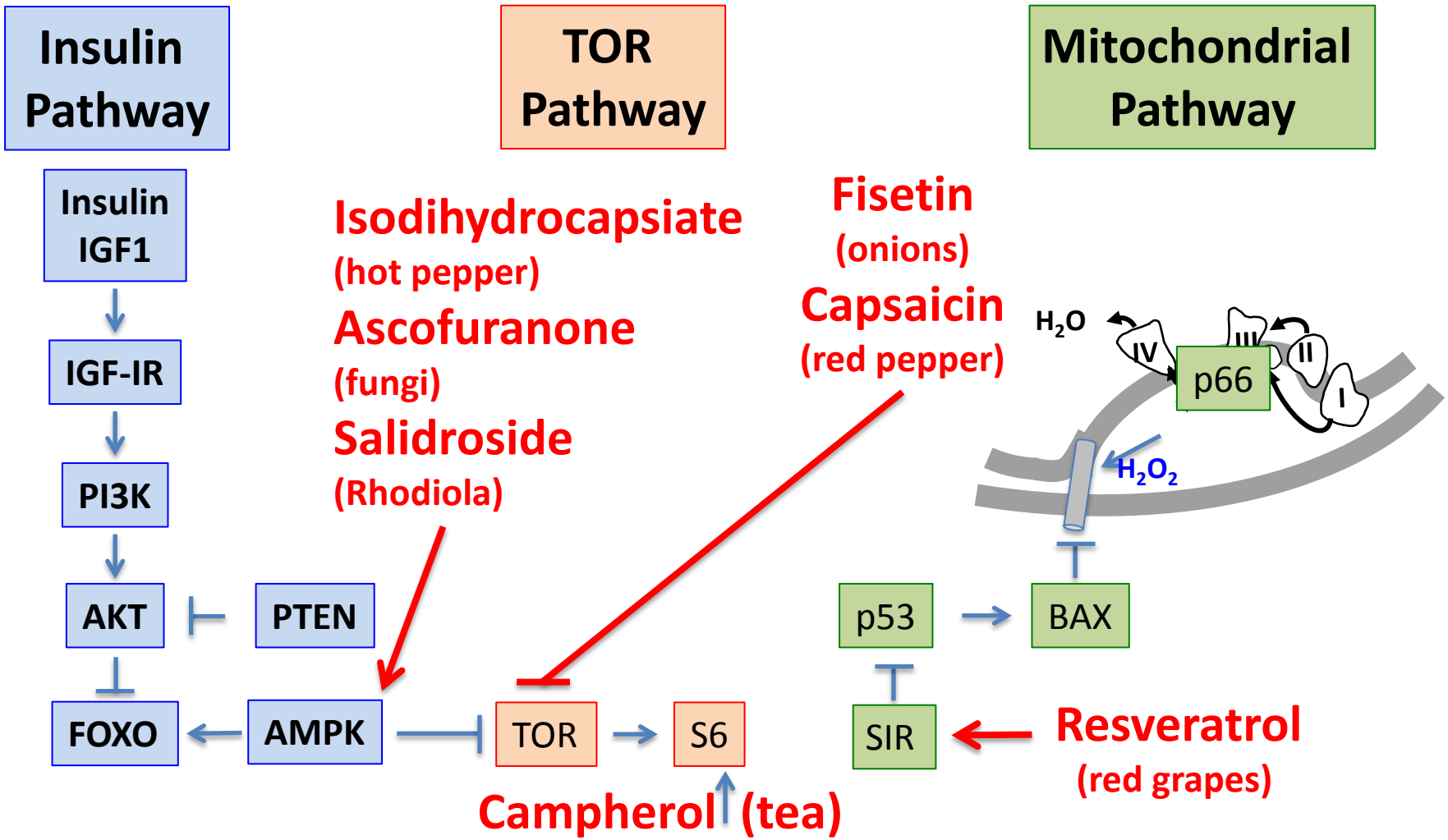




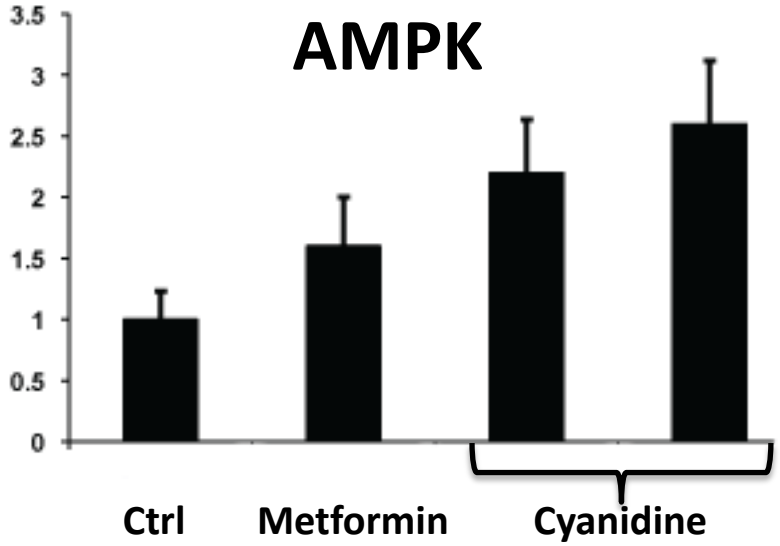
Can the identified pro-ageing pathways be manipulated to extend lifespan by pharmacological means?

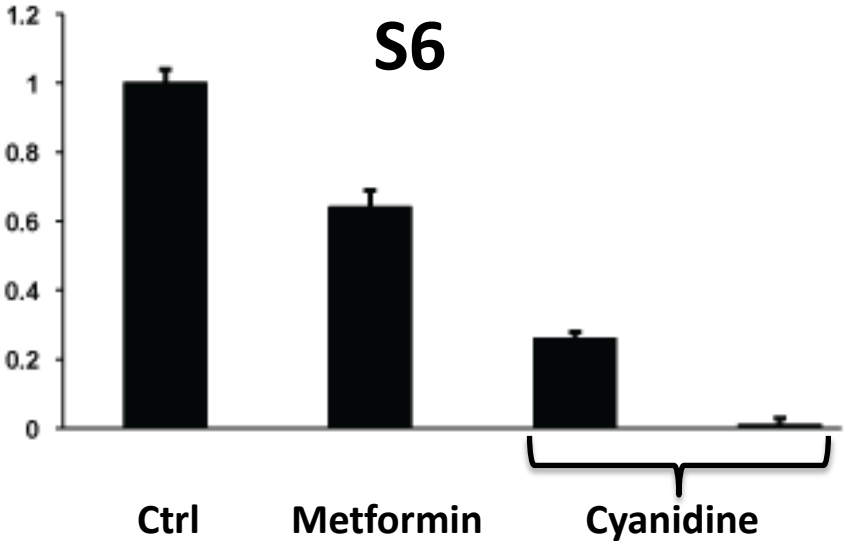


Many (CR mimetics) are found in plants



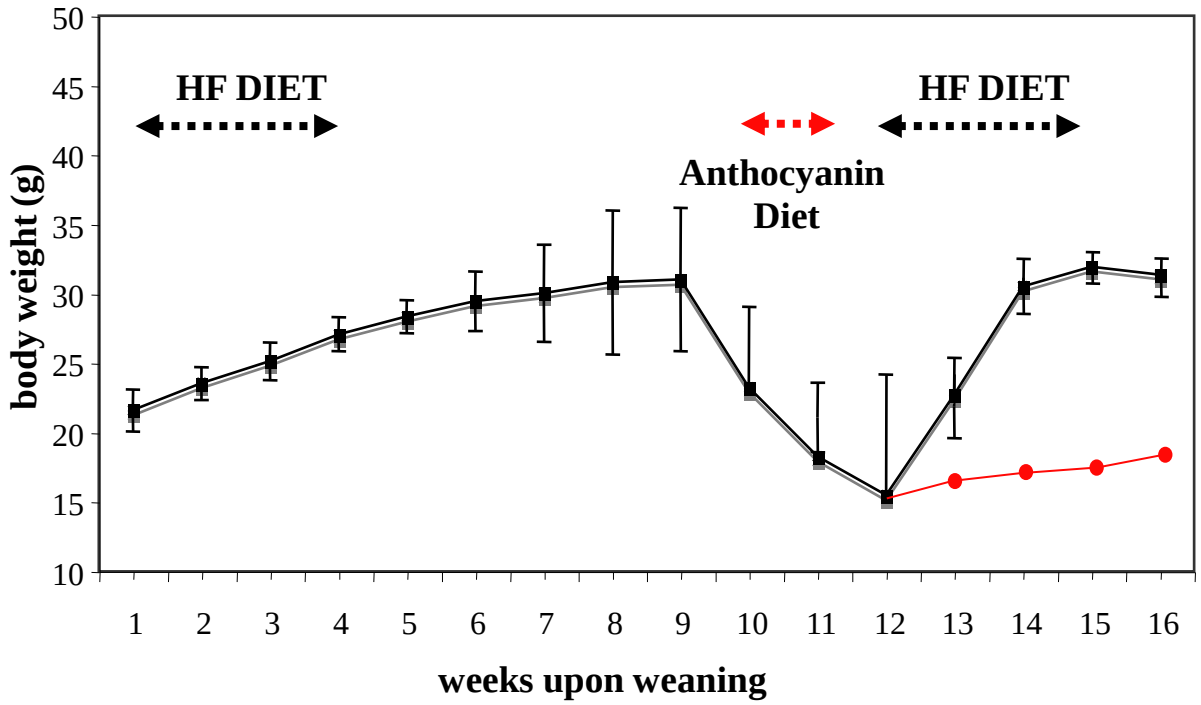
Anthocyanins (cyanidine)
(fruits, vegetables, pigmented cereals)

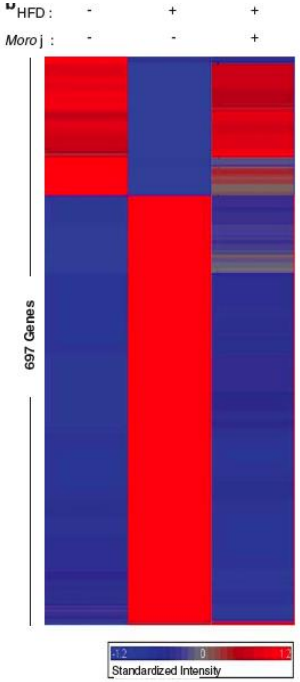




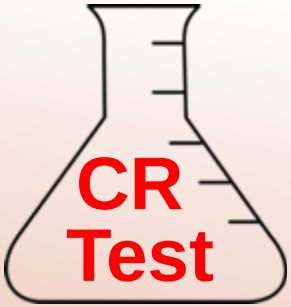
Blood-orange juice:

- **Reprograms metabolism**





- **Inhibits fat accumulation in mice**
- **Decreases heart ischemia/reperfusion injury**



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