Fourth World Conference on the Future of Science

Food and Water for Life

September 24th-27th, 2008
Venezia, Italy

Food, life span regulation and cancer

(*Italian Association for Cancer Research Lecture*)

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IEO
Istituto Europeo di Oncologia

Life-span is genetically determined

The aging process is influenced by both genetic and environmental factors

- **Life expectancy in the record-holding country increased of ~2 folds in the last 200 years**

  1840: 45 years (Swedish women)
  2000: 85 years (Japanese women)

  driven mainly by improvements in sanitation, housing and education
  (environmental)

- **Maximal life span did not vary significantly**

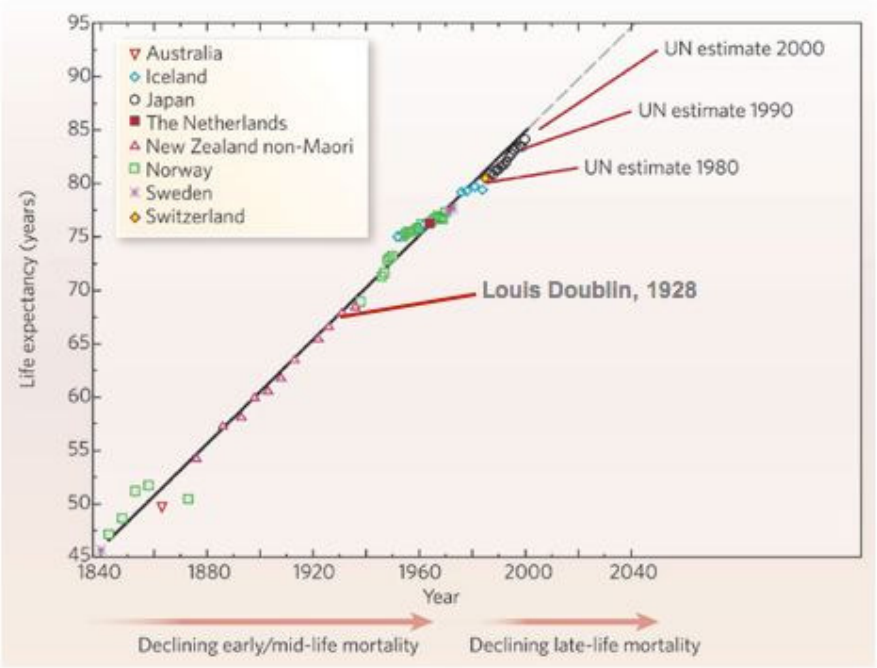
  due to the intrinsic limit of life-span, which become manifest under favorable condition
  (genetic)

Common belief:
the expectation of life
cannot rise much further.

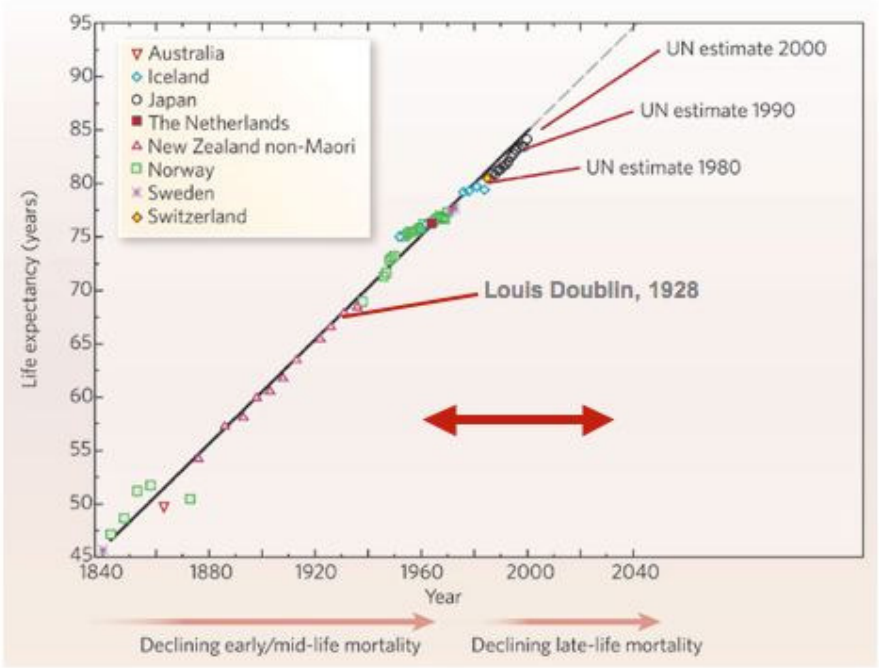
Prediction:
life-expectancy trajectories
will rapidly approach a maximum

(growth in longevity would stop
and we would see the fixed reality of the ageing process;
due to a fixed rate of mortality in the late-life)

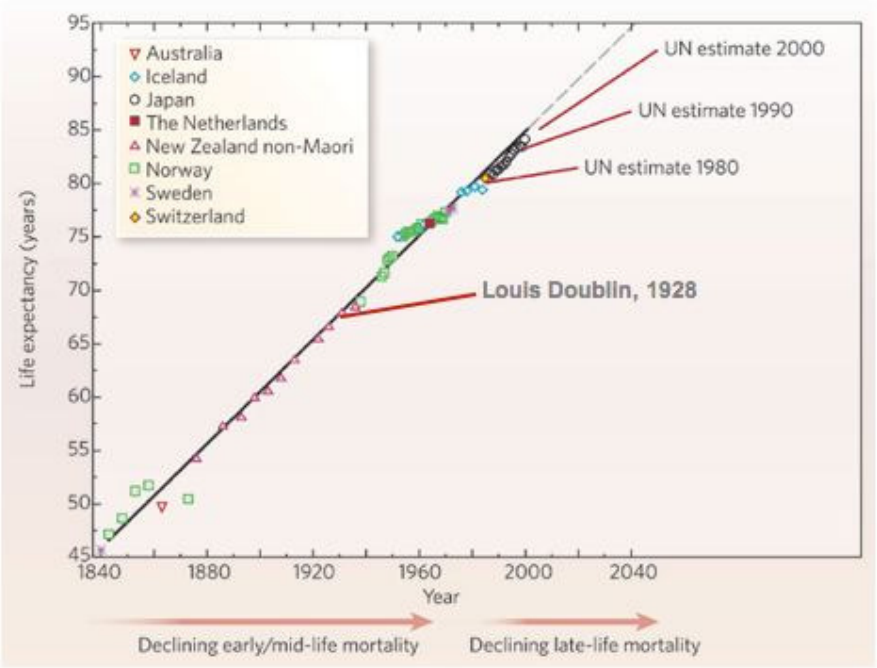
All forecasts have repeatedly been proven wrong (on the average 5 years after publication)



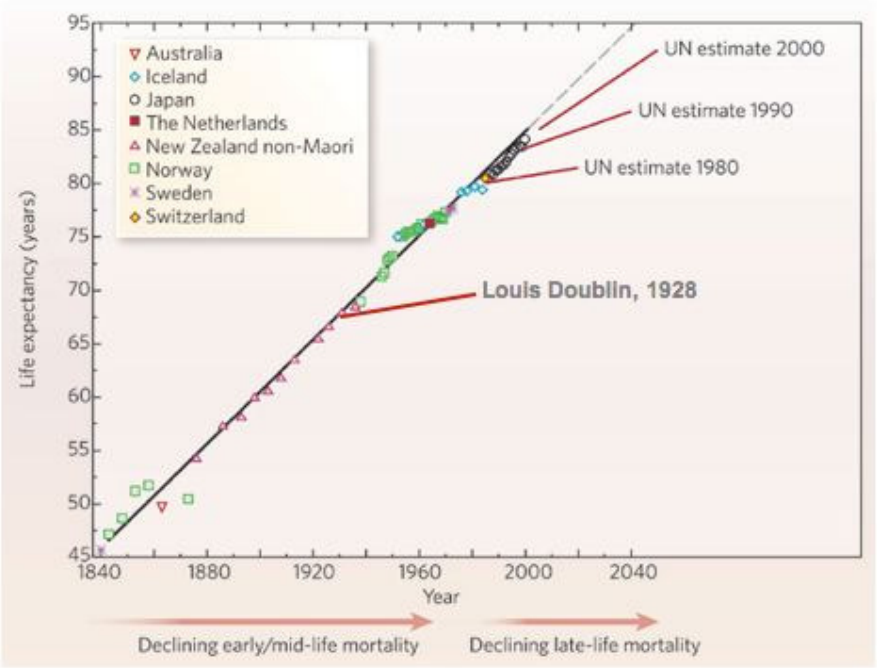
Life expectancy in developed countries has increased linearly in the last two centuries (and continued to increase linearly in the last 40 years)



As expected, no decline in early/mid-life mortality was observed in the last 40 years (in the developed countries)



Unexpectedly, a significant decline in early/mid-life mortality was observed in the last 40 years (in the developed countries)



Why life expectancy is still rising
In the western countries?

Where this process might end?

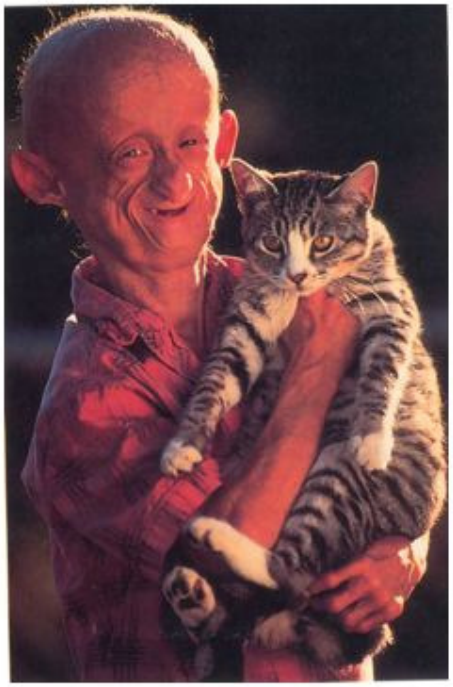
There is *no single accepted explanation*
or mechanism of aging
(more than 300 theories have been proposed)

Nascimur uno modo, multis morimu
(in one way we are born, in many ways we die,
and there is probably no single way to age)

Controversy reigns on whether aging
is the expression of
a specific *genetic program* (like development)
or a *non-programmed process* (wear-and-tear type)

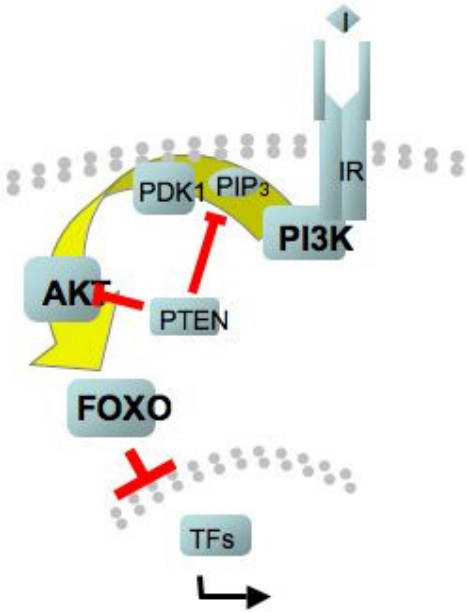
The case for programmed ageing:

- **Single gene mutations accelerate aging in humans**



18 year-old

- **Tens of single-gene mutations in model systems have been generated, which prolong life-span**



They all affect genes of the insulin pathway and attenuate insulin signaling

The metabolic theory of aging

Caloric restriction (w/o malnutrition) Prolongs life-span of multiple species, from single-celled organisms to mammals

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%
Rhesus	28%

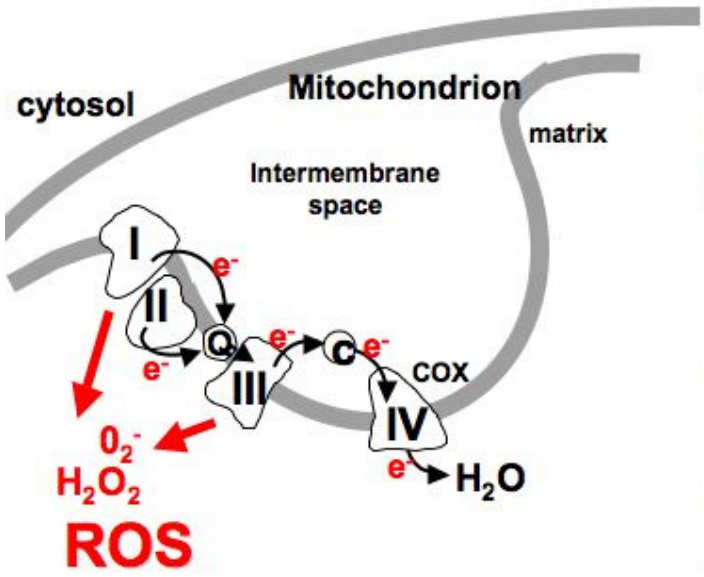
Insulin signaling in the *adipose tissue* regulates life-span in both invertebrates and mammals

- Caloric restricted mice have reduced adiposity
- Fat-specific disruption of the insulin receptor gene decreases body fat and prolongs life-span in mice

The case for no programme:

- **Natural selection could not, and would not, bring about such a fate**
- **Ageing is the simple consequence of a lifelong accumulation of *random molecular damage***
- **Damage is caused by free radicals (*Reactive oxygen species*; ROS)**

The free radical or mitochondrial theory of aging



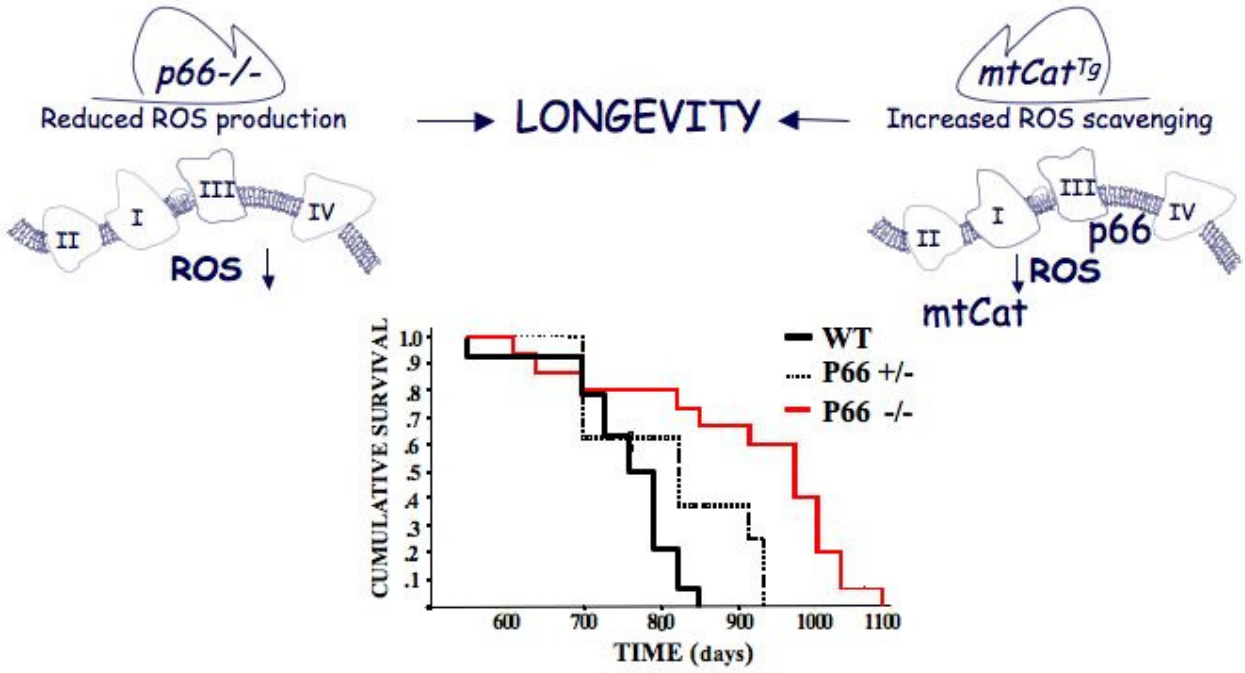
ROS are generated <u>accidentally</u>, as by-products of mitochondrial respiration (when molecular oxygen reacts with the ETC upstream to complex IV)

ROS induce damage to macromolecules (oxidative stress), which accumulates over life

Damaged macromolecules induce cell death (apoptosis) and tissue dysfunction

Oxidative stress → Cell death → Tissue degeneration

Genetic modifications that reduce levels of intracellular ROS prolong life-span



Two main life-span determinants:

- Insulin signaling in the fat tissue
- Oxidative stress

Two main interpretation of the aging process:

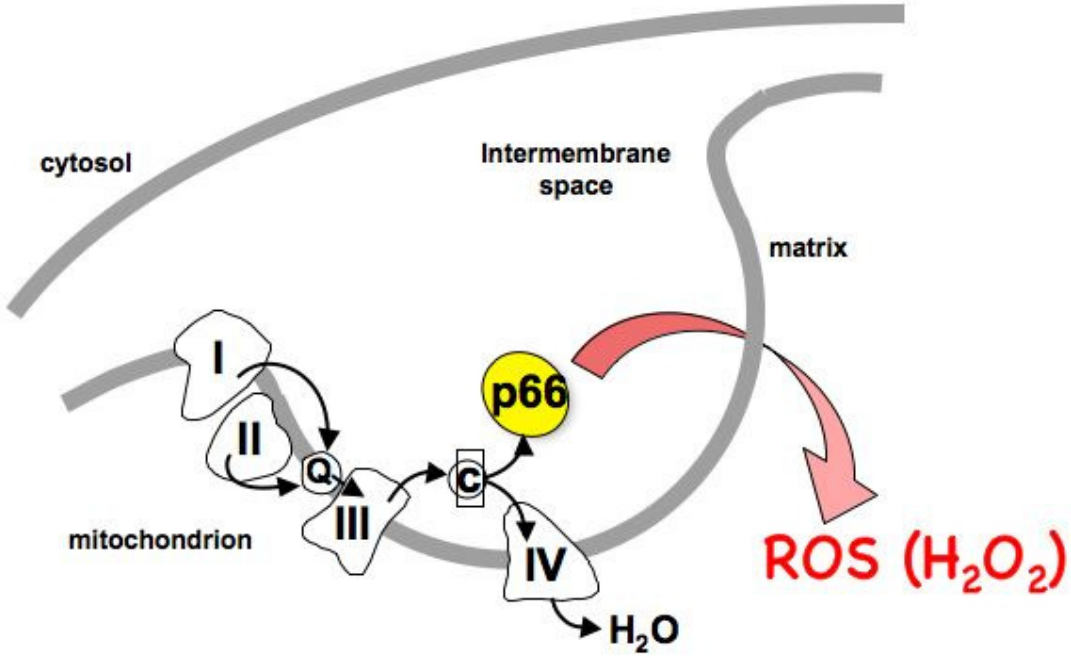
- Genetically programmed (deterministic)
- Unprogrammed (stochastic)

Do they represent alternative mechanisms and alternative interpretation?

One particular ROS (hydrogen peroxide; H_2O_2) behaves as a signaling molecule

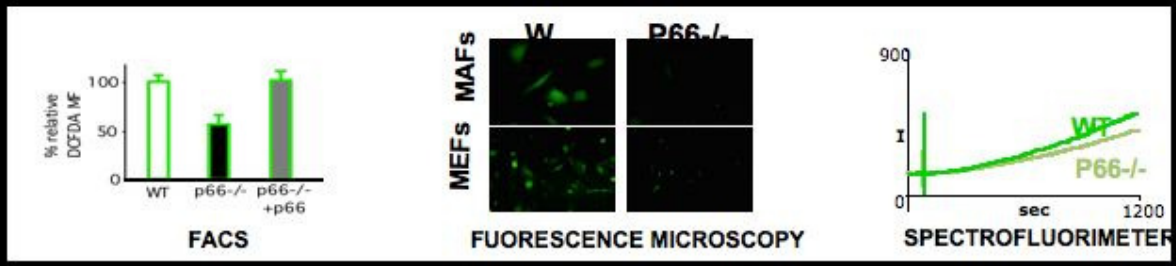
- **Induces fully reversible protein modifications**
  (e.g. oxidation of cysteinyl thiol with formation of disulphide bonds)
- **H_2O_2-induced modifications affect the function of the protein targets**
  (inactivation of phosphatases, activation of tyrosine kinases and of various transcription factors)
- **H_2O_2 potentiates receptor signaling (including insulin signaling)**

H_2O_2 can be generated in mitochondria by specialized enzymes (p66)

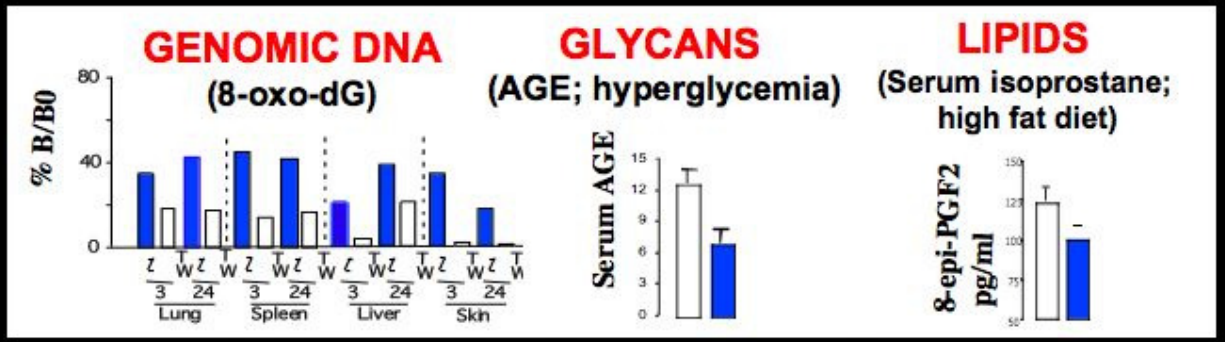


P66 functions as an inducible redox enzyme, which catalyzes the divalent reduction of O_2 to H_2O_2

P66 DELETION DECREASES INTRACELLULAR ROS



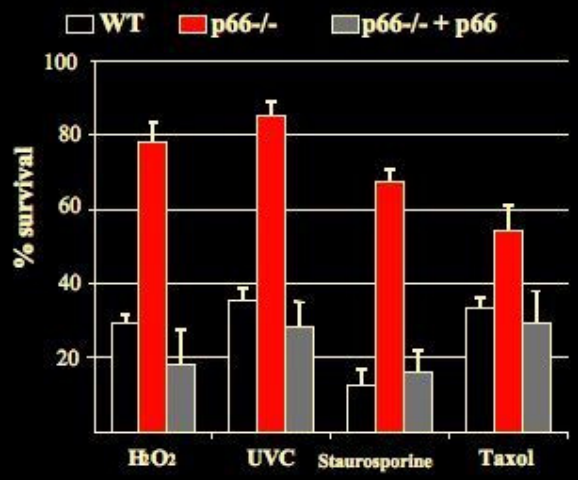
...SYSTEMIC OXIDATIVE STRESS..



Oncogene. 2002. 21:3872-8; Science. 2002. 295:2450-52; Mol Cell Biol. 2004. 24:1747-57; Circulation. 2004. 109:2917-23

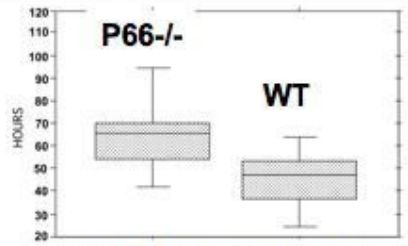
INCREASED RESISTANCE TO STRESS-INDUCED APOPTOSIS IN MICE WITH DELETION OF P66

IN VITRO

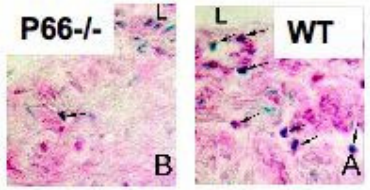


Nature. 1999. 402:309-13
Oncogene. 2002. 21:3872-8
Mol Cell Biol. 2004. 24:1747-57
J Biol Chem. 2004. 279:25689-95
Circulation. 2004. 109:2917-23
J Cell Biol. 2005.169:331-9
Endocrinology. 2005. 146:1498-505
Apoptosis. 2005. 10:13-18

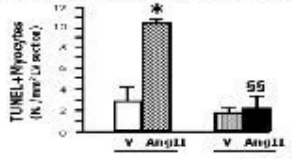
IN VIVO



PARAQUAT TOXICITY (LUNG)



HYGH FAT DIET (VESSELS)

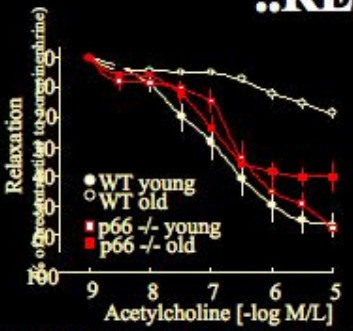


WT P66-/-

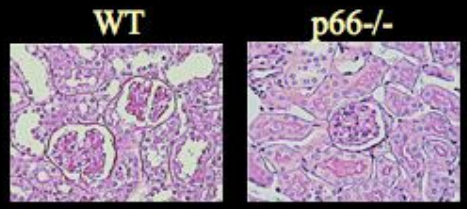
ANGIOTENSIN II (HEARTH)

Nature. 1999. 402:309-13
Proc Natl Acad Sci USA. 2003. 100:2112-6
Circulation. 2004. 109:2917-23
Hypertension. 2005. 46:433-40
Cell. 2005. 122:221-33

..RETARDES AGEING..

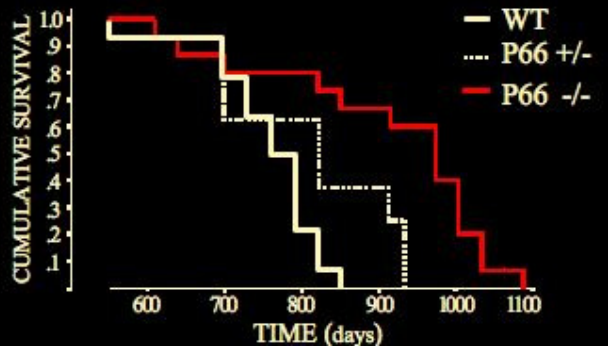


AORTA RELAXATION IS IMPAIRED
IN AGED WT BUT NOT IN P66-/- MICE

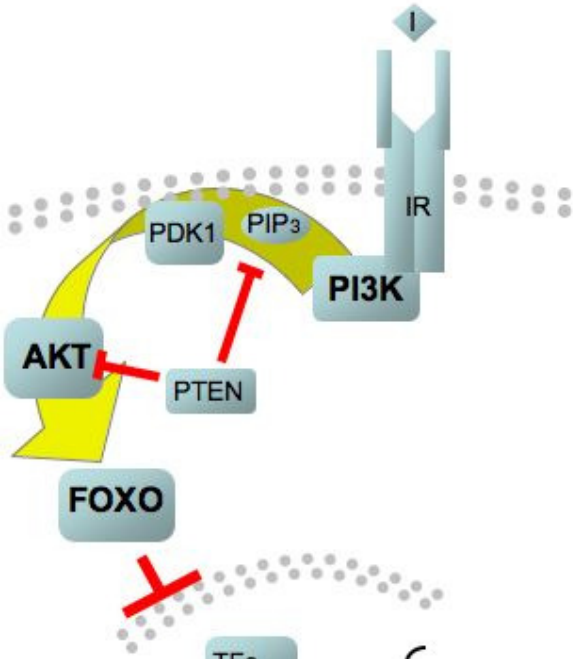


GLOMERULAE VOLUME INCREASES
IN AGED WT BUT NOT IN P66-/- MICE

..AND PROLONGS LIFE SPAN



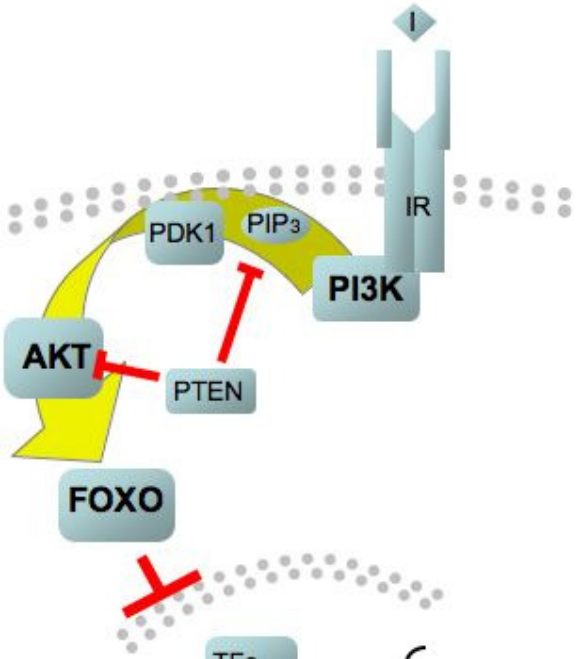
Nature. 1999. 402:309
Circulation. 2004. 110:2889
Diabetes. In p



Analyses of the effcets of P66 on insulin signaling In the adipose tissue

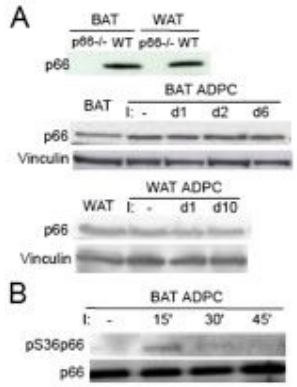
Fatty Acid Oxidation → TG accum.

Glucose uptake



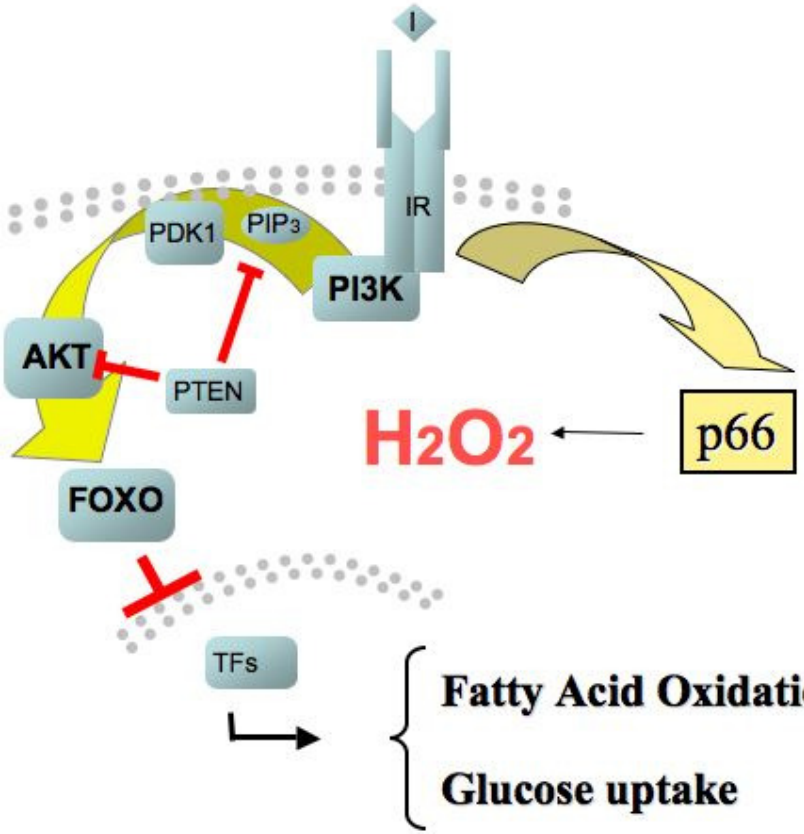
P66 is expressed in the white and brown adipose tissue

p66

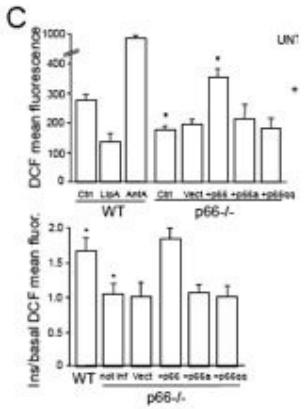


Fatty Acid Oxidation → **TG accum.**

Glucose uptake

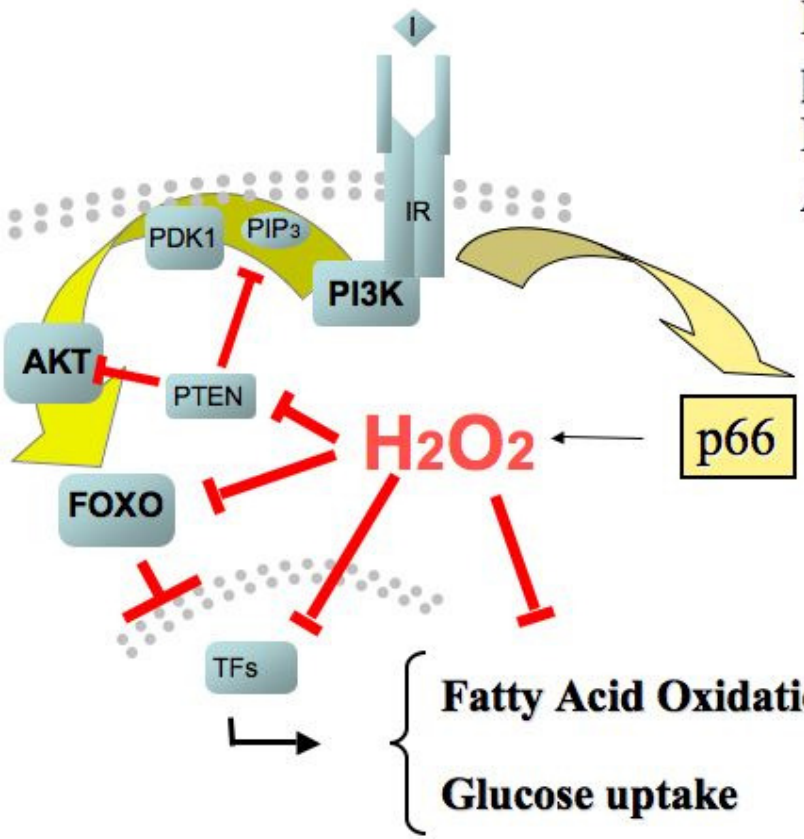


P66 produces H_2O_2 in the adipose tissue after insulin treatment

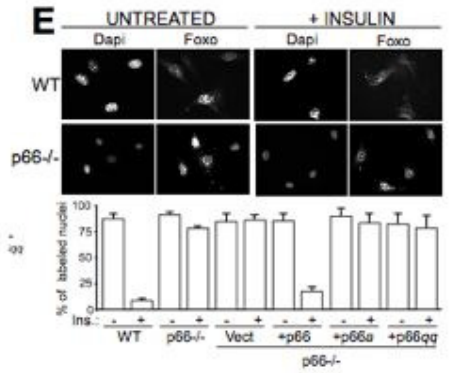


Fatty Acid Oxidation → **TG accum.**

Glucose uptake

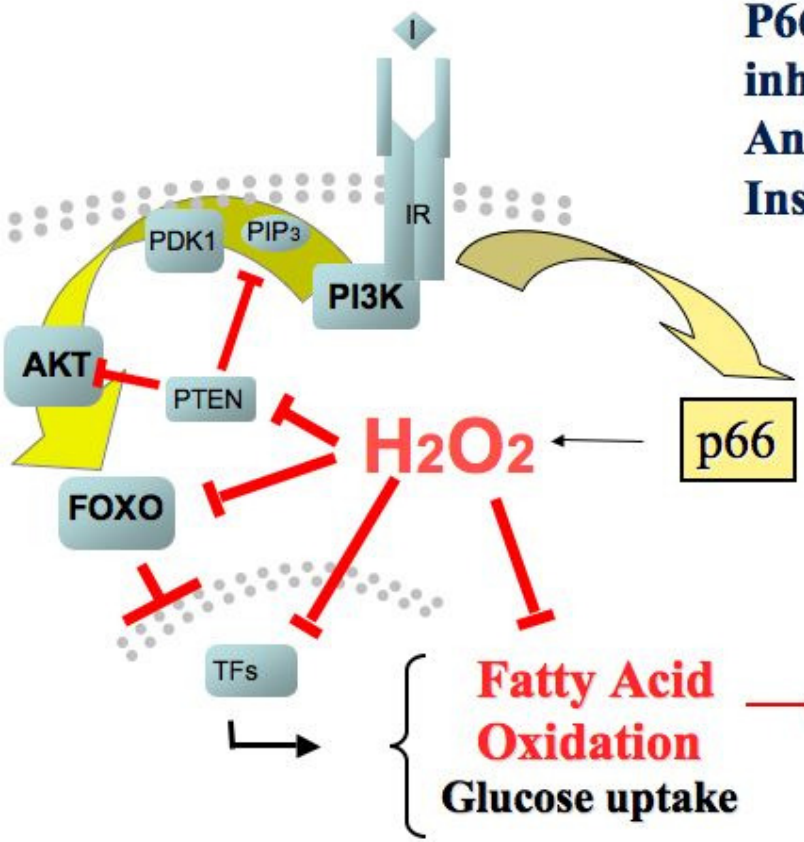


P66-generated H2O2 potentiates Insulin signaling At multiple levels

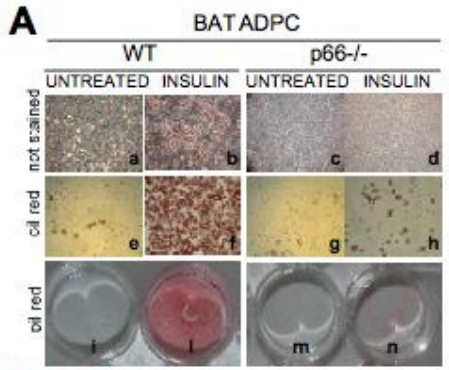


Fatty Acid Oxidation → **TG accum.**

Glucose uptake

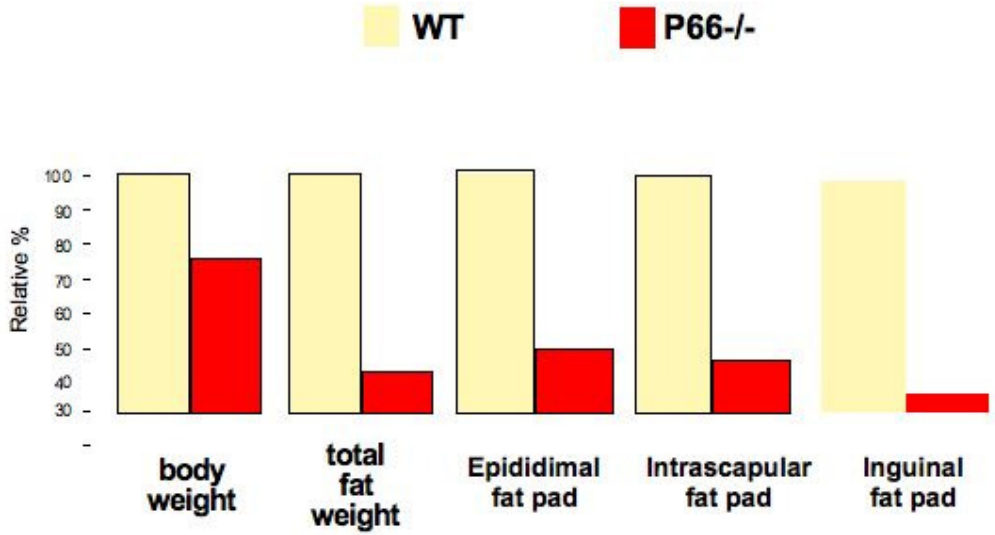


P66-generated H2O2
inhibits fatty acid oxidation
And potentiates
Insulin-induced lipogenesis

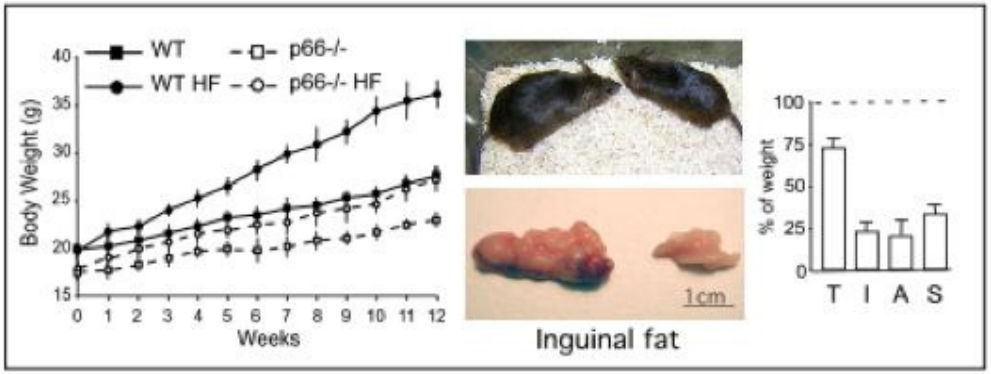


TG accum.

P66-/- mice have less Adipose Tissue

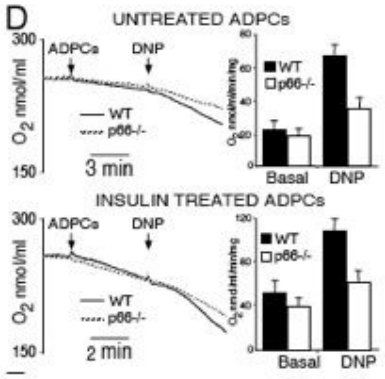


P66-/- mice are protected from diet-induced obesity

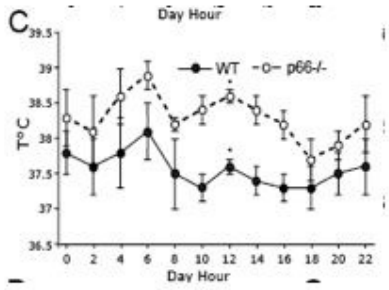


p66 is a genetic determinant of fat development in adult mice

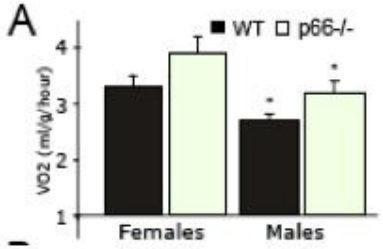
Analysis of metabolism: p66Shc favors energy conservation



Better mitochondrial coupling



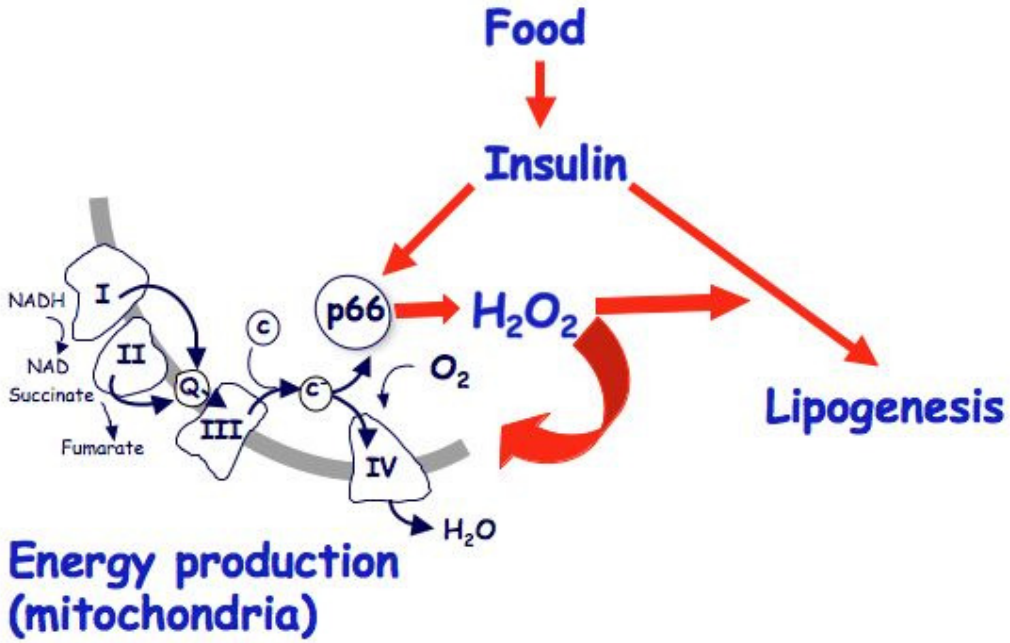
Increased basal body temperature



Higher energetic expenditure

In the p66Shc-/- mice

P66 switches the energetic balance of adipocytes toward lipogenesis and energy conservation

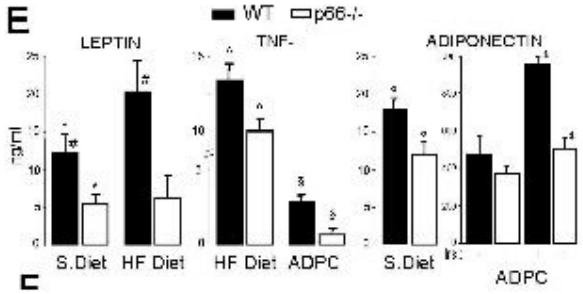


P66 exerts this function by integrating, in adipocytes, insulin-signaling and mitochondrial energetic state

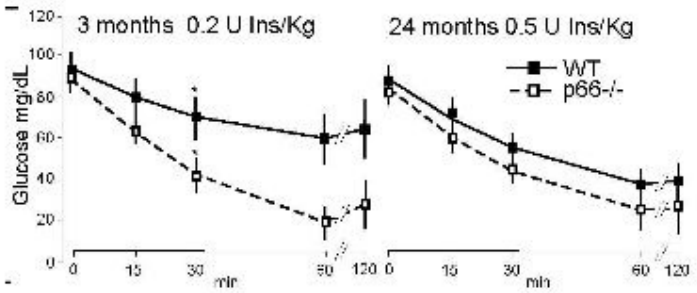
Does reduced adiposity play a role in the effect of p66 on life-span?

- CR and FIRKO mice have reduced adiposity and live longer
- CR and FIRKO mice have a relative increase of the systemic sensitivity to insulin
- Aging is associated with the development of relative insulin resistance

P66 “decreases” insulin sensitivity

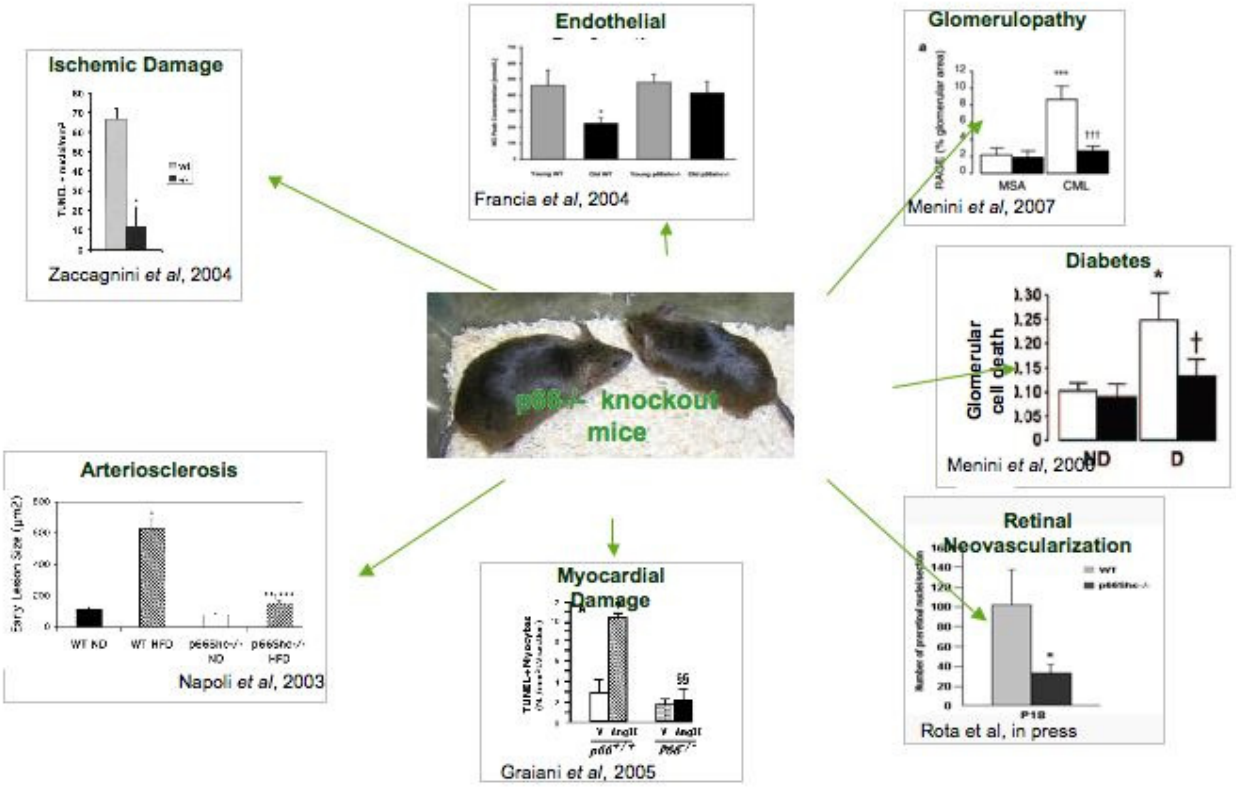


Reduced adipokine secretion In the p66-/- mice



And increased insulin sensitivity

Reduced severity of late-onset (degenerative) diseases in p66-null mice



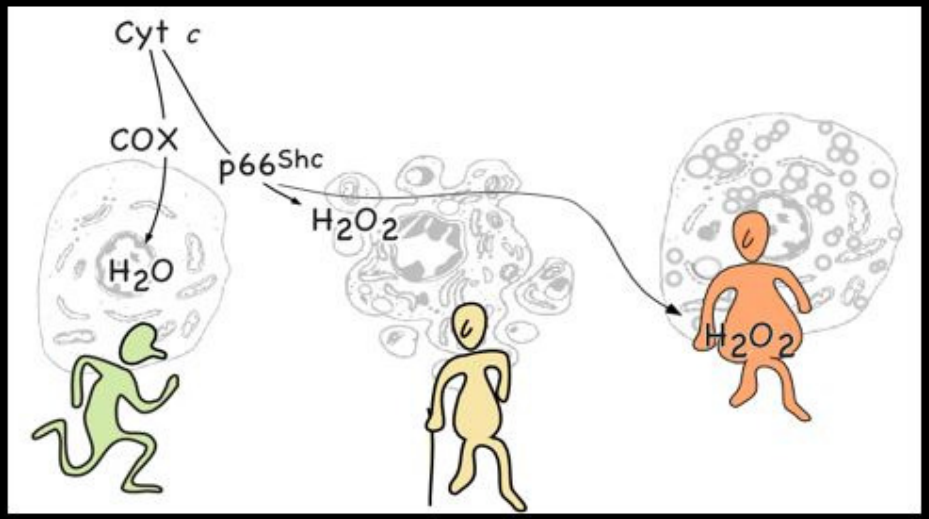
P66^{Shc} is a genetic factor of the metabolic syndrome

P66 -/- mice show:

- Increased insulin sensitivity
- Higher glucose tollerance
- Reduced body weight
- Reduced fat mass
- *low risks of endothelial disfunction*
- *low risk of atherosclerosis*

The **METABOLIC SYNDROME** includes:

- Insulin resistance
- Glucose intolerance
- Hyperglicemia
- Obesity/Excessive fat tissue
- Atherogenic dyslipidemia, higher risk of atherosclerosis
- *Raised blood pressure*
- *Prothrombotic state*
- *Proinflammatory state*



$p66^{Shc}$-generated H_2O_2 regulates directly the threshold of sensitivity to insulin in adipocytes (and indirectly the penetrance of aging-associated diseases) and the development of fat tissue

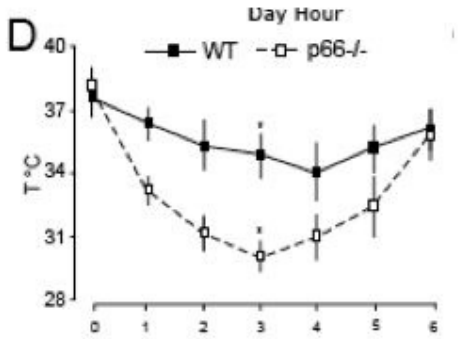
Why p66 *increases* the treshold of insulin sensitivity?

Why mammals are "*more obese*" than needed?

Why mammals have a genetic program that increases The risk of disease?

How the p66 program was selected during evolution?

Abnormal adaptation to cold in p66-/- mice



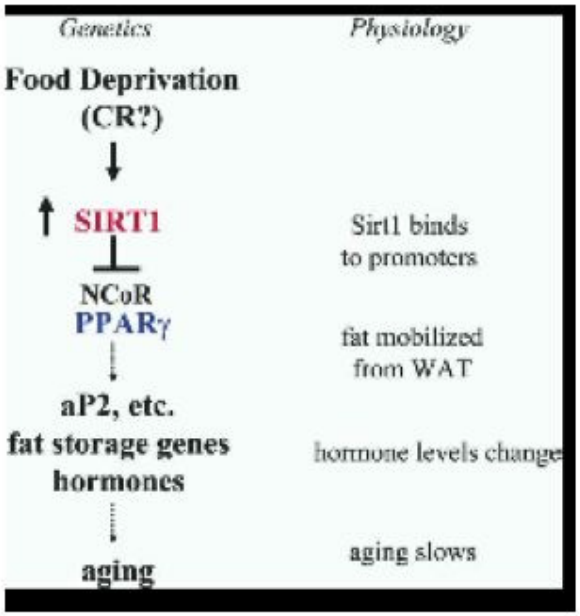
(accelerated heat loss due to reduced thermal insulation)

The physiological size of the fat tissue may be set to serve other functions, which are evolutionarily more critical than longevity.

Adaptation to cold and/or optimization of energy storage when food is available could be one of such functions

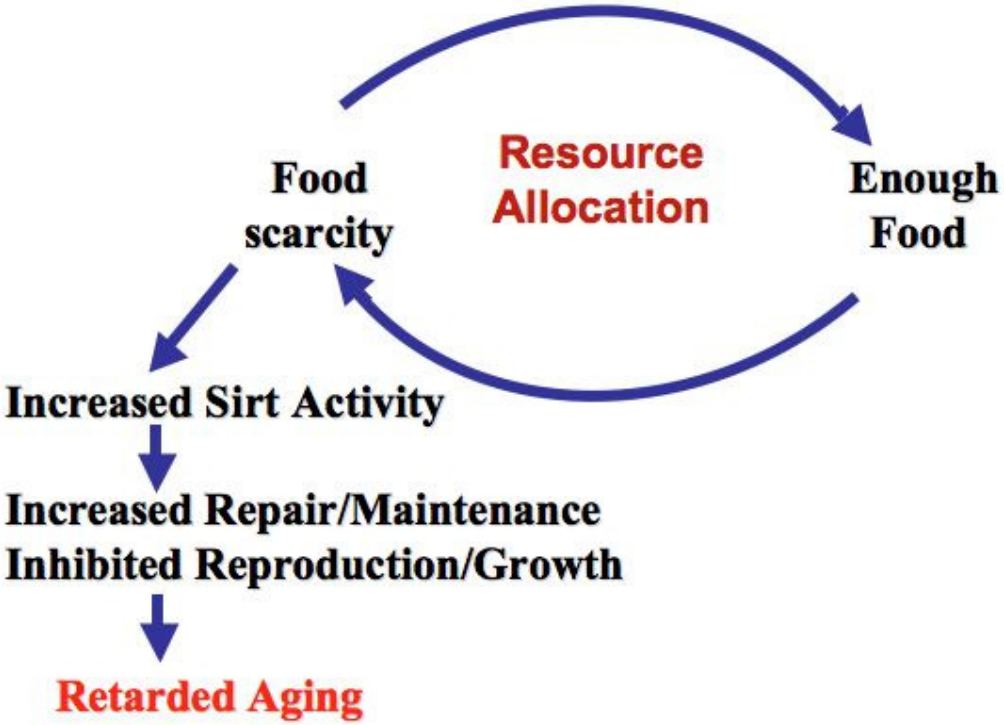
Why such functions are mechanistically linked to life span control?

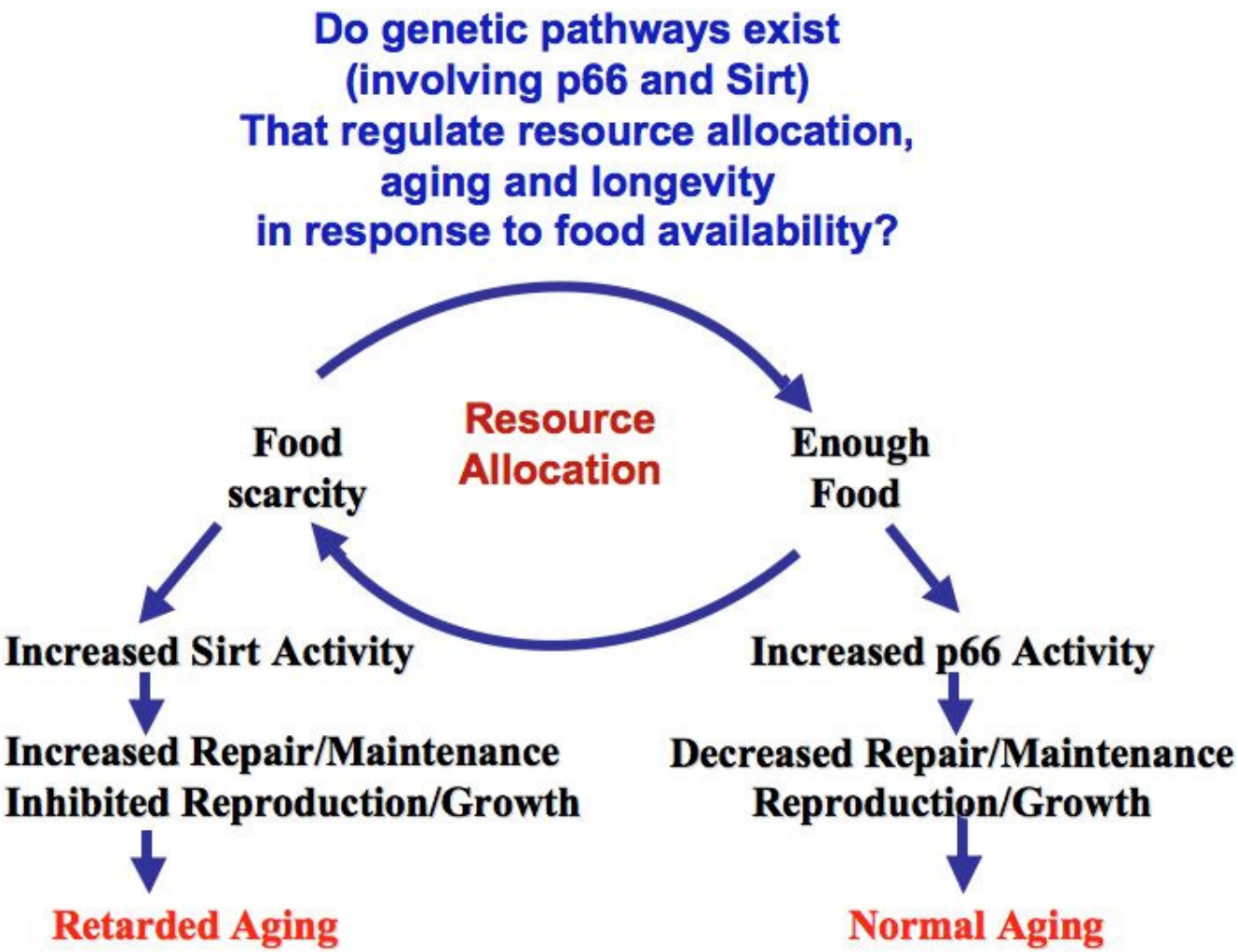
A conserved genetic pathway (yeast, worms, flies, mammals) That is activated by food scarcity and that retards aging

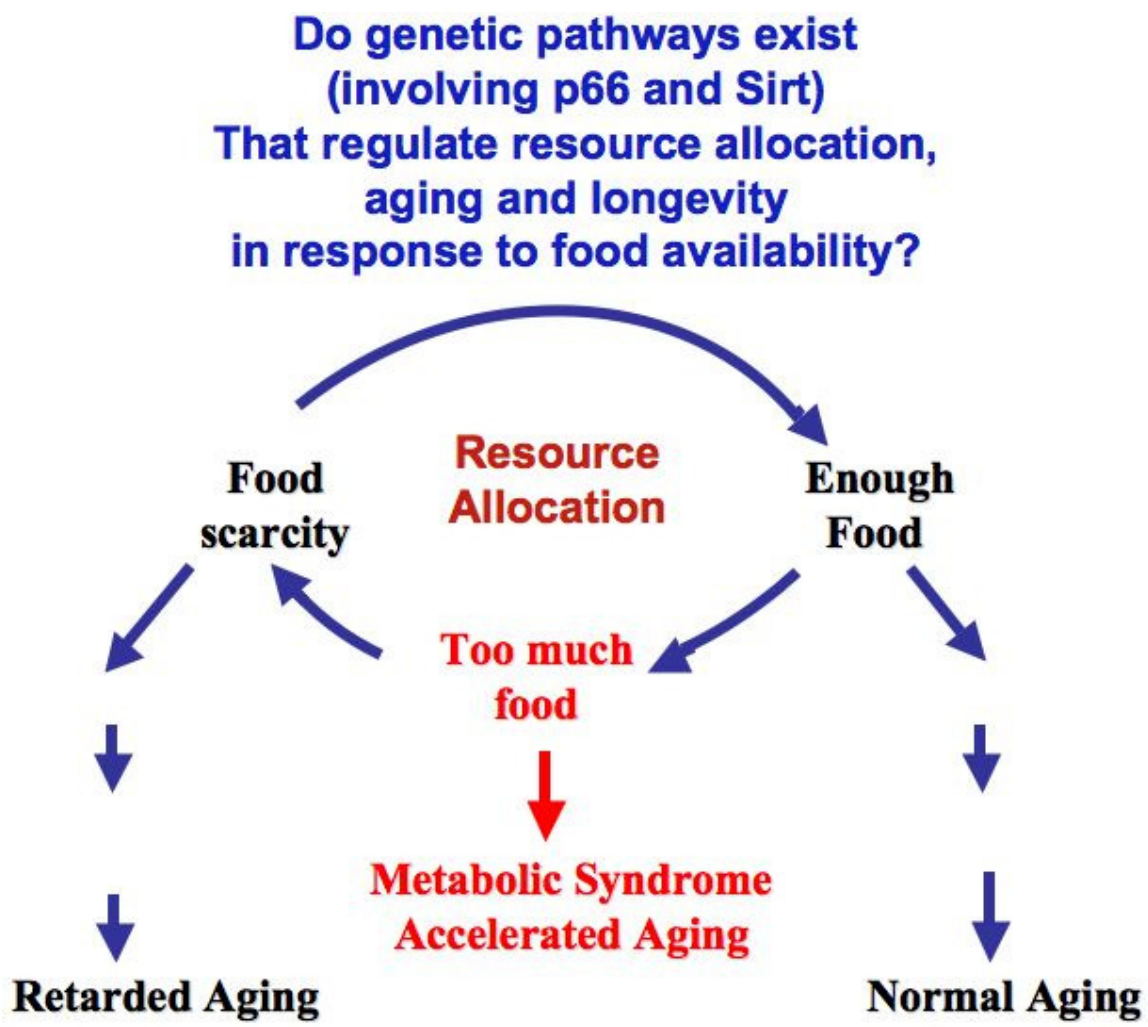


(L. Guarente, 2006)

Do genetic pathways exist
(involving p66 and Sirt)
That regulate resource allocation,
aging and longevity
in response to food availability?




Do genetic pathways exist
(involving p66 and Sirt)
That regulate resource allocation,
aging and longevity
in response to food availability?
Food
scarcity
Resource
Allocation
Enough
Food
Increased Sirt Activity
Increased Repair/Maintenance
Inhibited Reproduction/Growth
Retarded Aging
Increased p66 Activity
Decreased Repair/Maintenance
Reproduction/Growth
Normal Aging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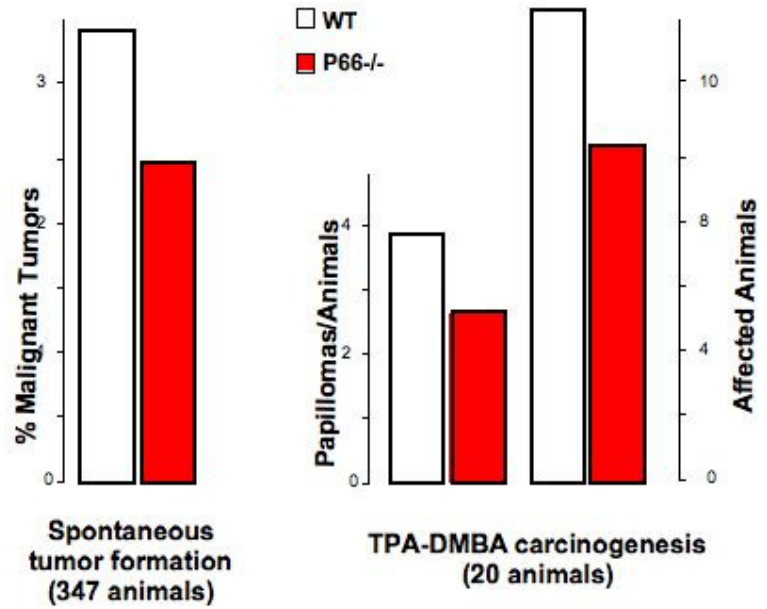
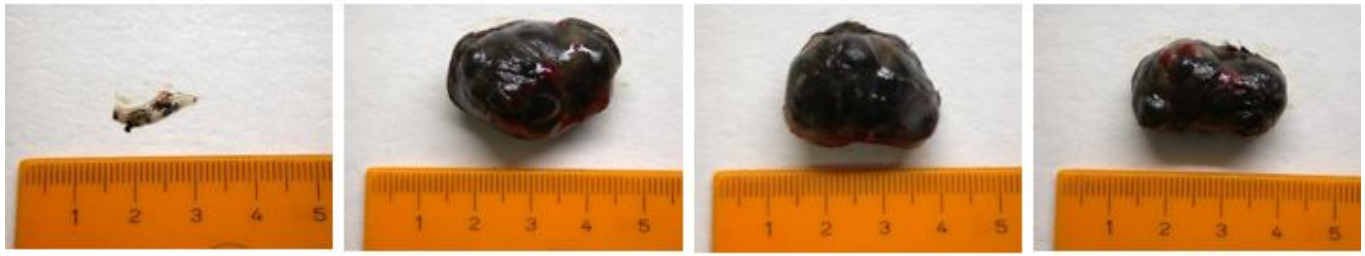
That regulate resource allocation,
aging and longevity
in response to food availability?
Resource
Allocation
Food
scarcity
Enough
Food
Too much
food
Metabolic Syndrome
Accelerated Aging
Retarded Aging
Normal Aging

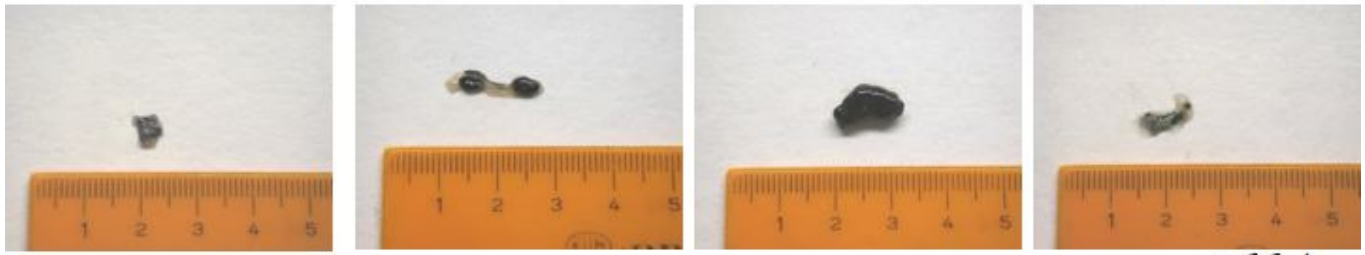
Decreased tumor formation in the p66-/- mice



Reduced B16F1melanoma growth in p66Shc-/- female mice



WT



p66-/-

Obesity and insulin resistance Are important cancer-risk factors

1. Obesity and diabetes are cancer risk factors

Epidemiological and animal studies have shown that overweight and obesity ***(BMI>5Kg/m2***) are associated with ***increased risk for cancers at numerous sites***, including the breast (among postmenopausal women), colon, endometrium, esophagus, gallbladder, liver, prostate, ovarian, pancreas, and kidney. A recent study of approximately 900,000 individuals suggests that **obesity may account for *14% of cancers in men and 20% of cancers in women***, and in this cohort, the heaviest men and women were ***52% and 62%,*** respectively, more likely to die of cancer.

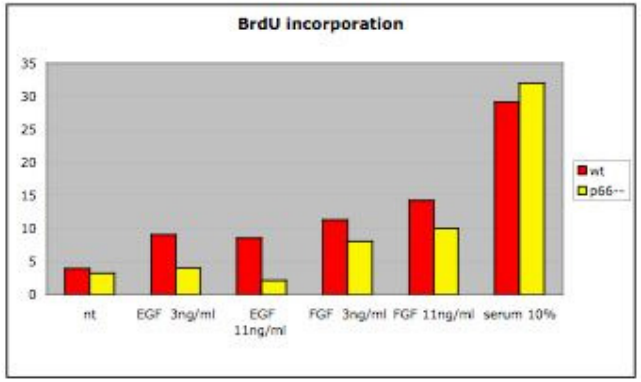
2. Insulin-resistance is a cancer risk factor (independent, with respect to obesity and diabetes)

Adults with ***impaired glucose tolerance*** have the greatest adjusted relative hazard of cancer mortality (relative hazard = 1.87, 95% confidence interval (CI): 1.06, 3.31), followed by those with ***undiagnosed diabetes*** (relative hazard = 1.31, 95% CI: 0.48, 3.56) and ***diabetes*** (relative hazard = 1.13, 95% CI: 0.49, 2.62).

Putative mechanisms of the reduced cancer risk in the p66-/- mice

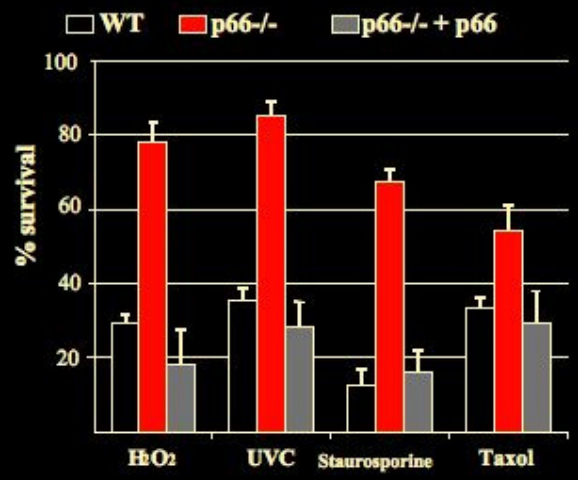
- **Decreased secretion pro-inflammatory and tumor-promoting adipokines**

- **Decreased cellular sensitivity to tumor-promoting hormones (Insulin and IGF-1)**



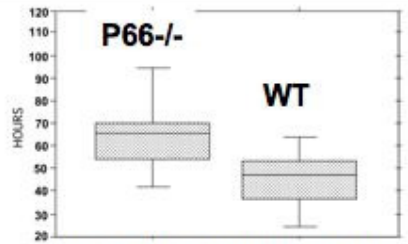
INCREASED RESISTANCE TO STRESS-INDUCED APOPTOSIS IN MICE WITH DELETION OF P66

IN VITRO

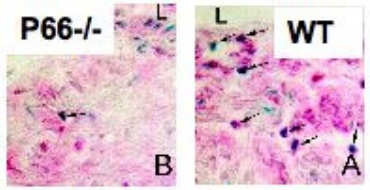


Nature. 1999. 402:309-13
Oncogene. 2002. 21:3872-8
Mol Cell Biol. 2004. 24:1747-57
J Biol Chem. 2004. 279:25689-95
Circulation. 2004. 109:2917-23
J Cell Biol. 2005.169:331-9
Endocrinology. 2005. 146:1498-505
Apoptosis. 2005. 10:13-18

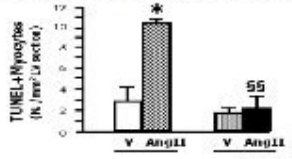
IN VIVO



PARAQUAT TOXICITY (LUNG)



HYGH FAT DIET (VESSELS)

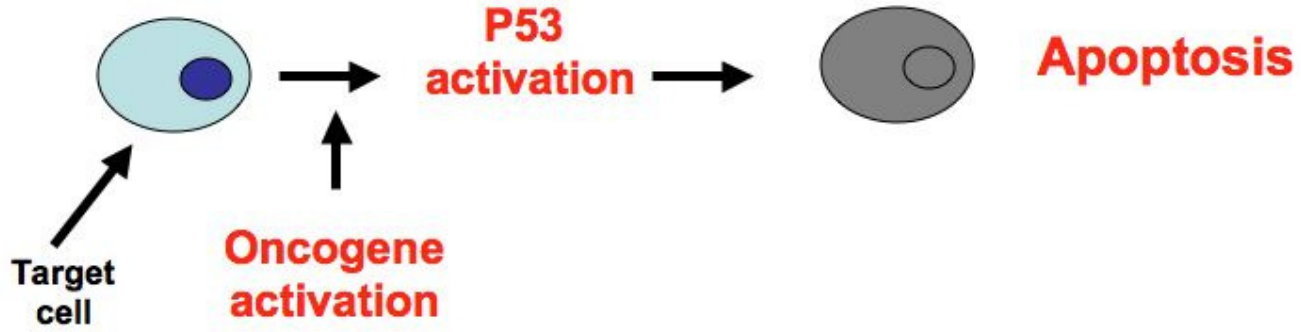


WT P66-/-

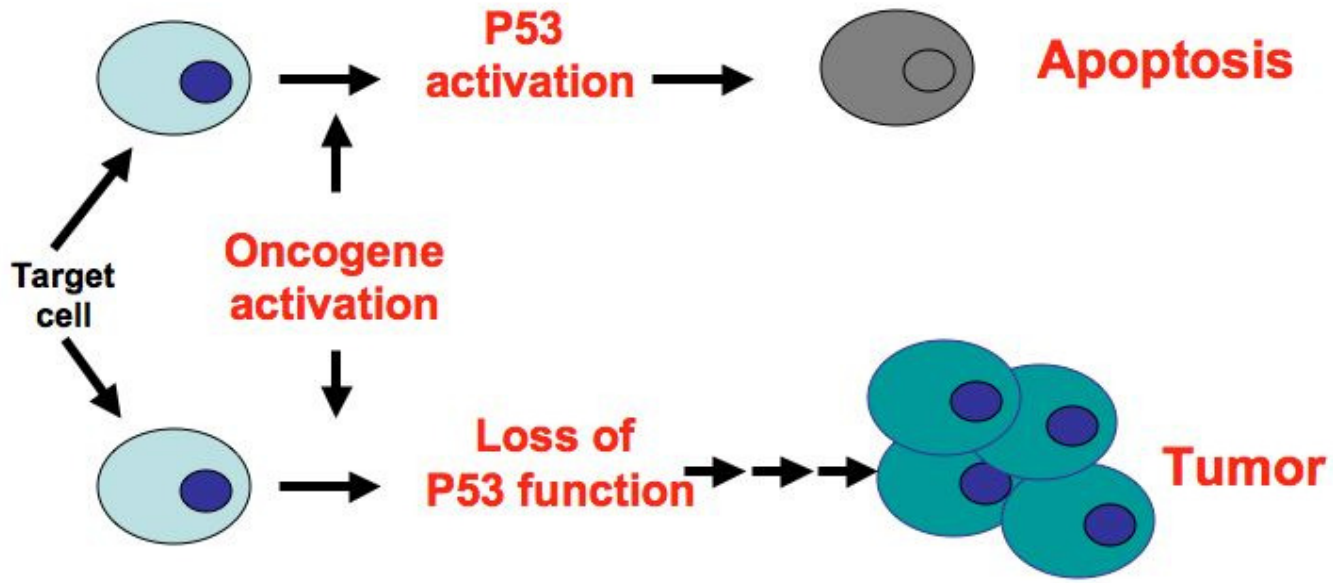
ANGIOTENSIN II (HEARTH)

Nature. 1999. 402:309-13
Proc Natl Acad Sci USA. 2003. 100:2112-6
Circulation. 2004. 109:2917-23
Hypertension. 2005. 46:433-40
Cell. 2005. 122:221-33

Apoptosis is the most powerful mechanism of tumor suppression



Apoptosis is the most powerful mechanism of tumor suppression



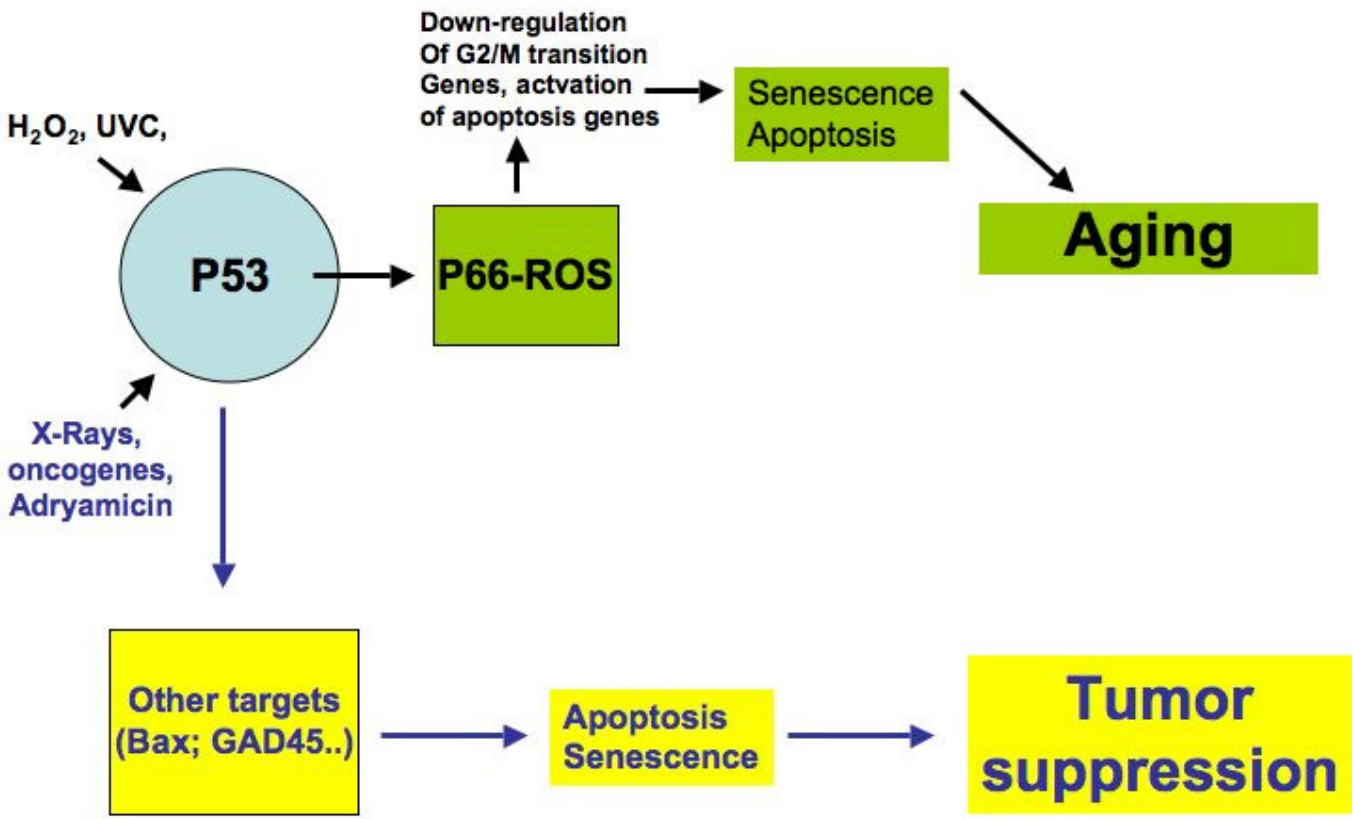
Longevity mouse models:

IGF1R+/-; Ames Dwarf;
GHR-/-; p66Shc-/-;
caloric restriction

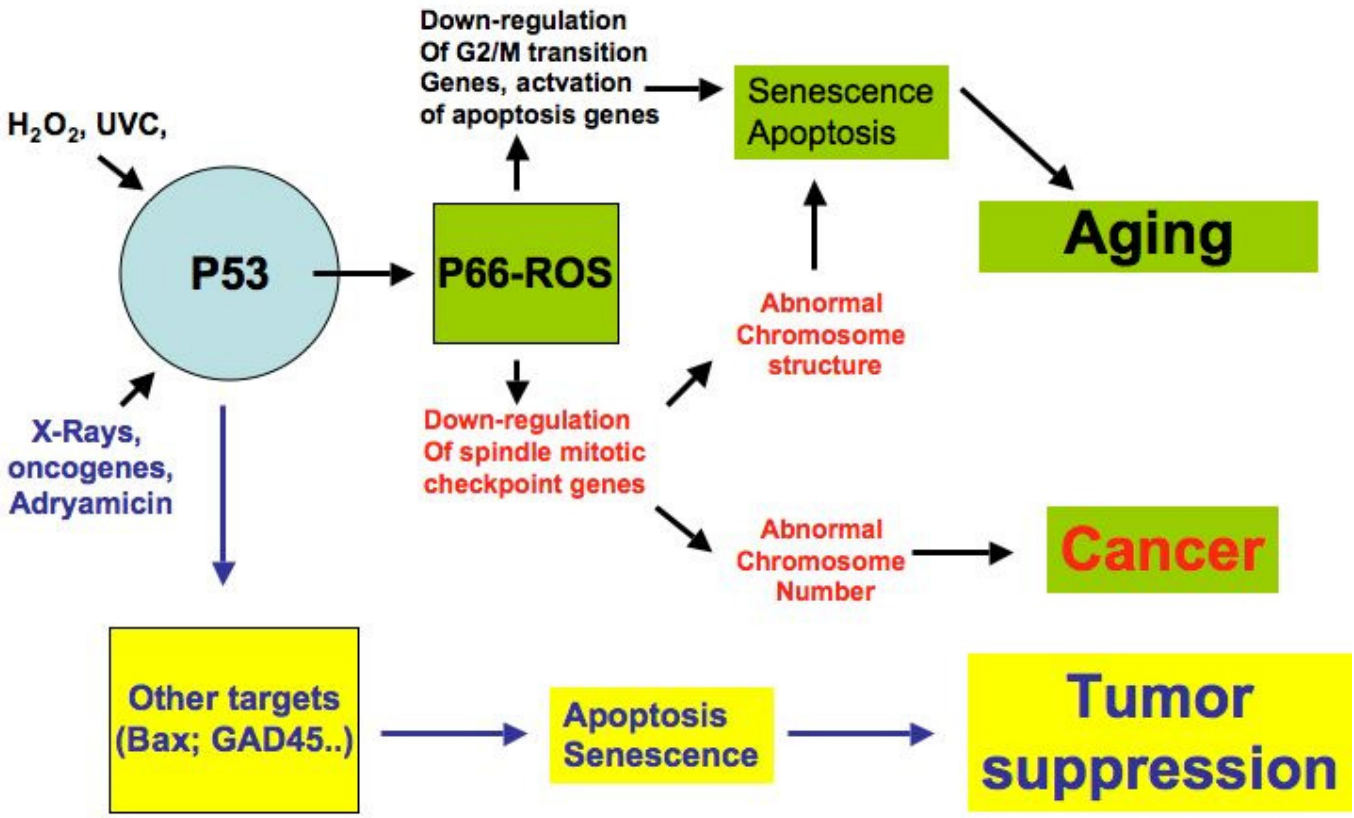
- **Increased resistance to stress (reduced apoptosis)**

- **No increased risk of tumor formation**

The p53-p66 pathways



The p53-p66 pathways



The p53-p66 pathway manifests its effects on tissue homeostasis (degeneration and transformation) late in life