Convergent and Divergent Mechanisms in Aging and Cancer

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LEARNING OBJECTIVES

1. To identify convergent and divergent mechanism between aging and cancer

2. To learn the pathways that regulate aging and cancer

3. To study the effects of caloric restriction in longevity and cancer

AGING

-An old concept linked growing old=decline.

-The accumulation of damage to molecules, cells and tissues over a lifetime, often leads to frailty and malfunction.

-Increase risk factor for many diseases like cancer, cardiovascular and neurodegenerative diseases.

-A new concept: Aging process is subjected to regulation by classical signaling pathways and transcription factors.

-Aging is regulated by specific genes conserved from yeast to mice.

Regulation of Aging

-Mutations that extend lifespan affect stress-response genes or nutrient sensors.

-Excess of food: stress levels are low and genes support growth and reproduction.

-Harsh conditions: animal undergoes to a stage of cell protection and maintenance to protect it from environmental stress and it also extends lifespan.

-CR or DR was assumed to extend lifespan simply by reducing the rate at which cellular damage accumulates over time as a result of nutrient metabolism.

-Longevity response to CR is actively regulated by nutrients-sensing pathways involving the kinase mTOR, AMPK, sirtuins and IGF-1 signaling.

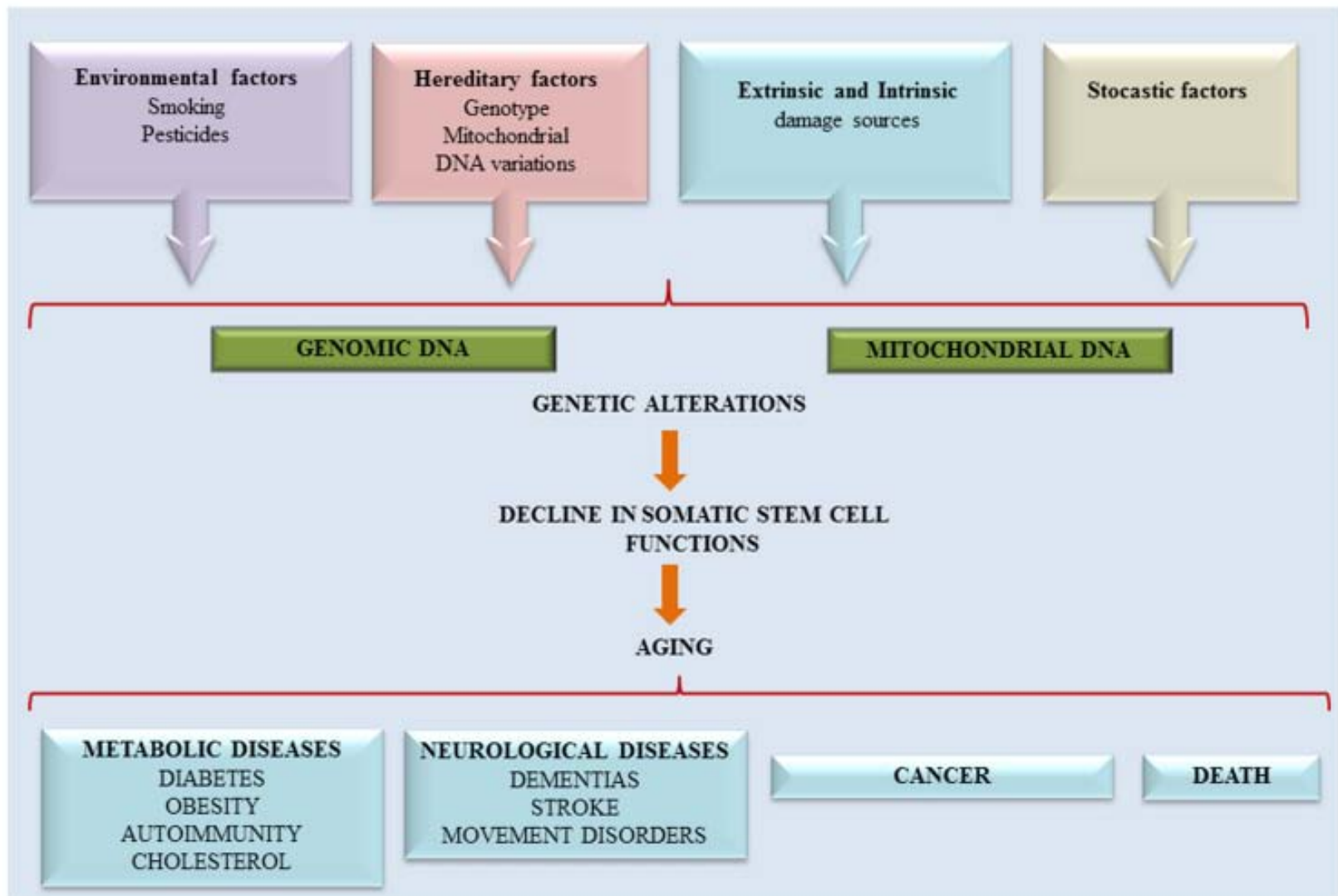# Insulin/IGF-1 and FOXO signaling affects mouse and human lifespan
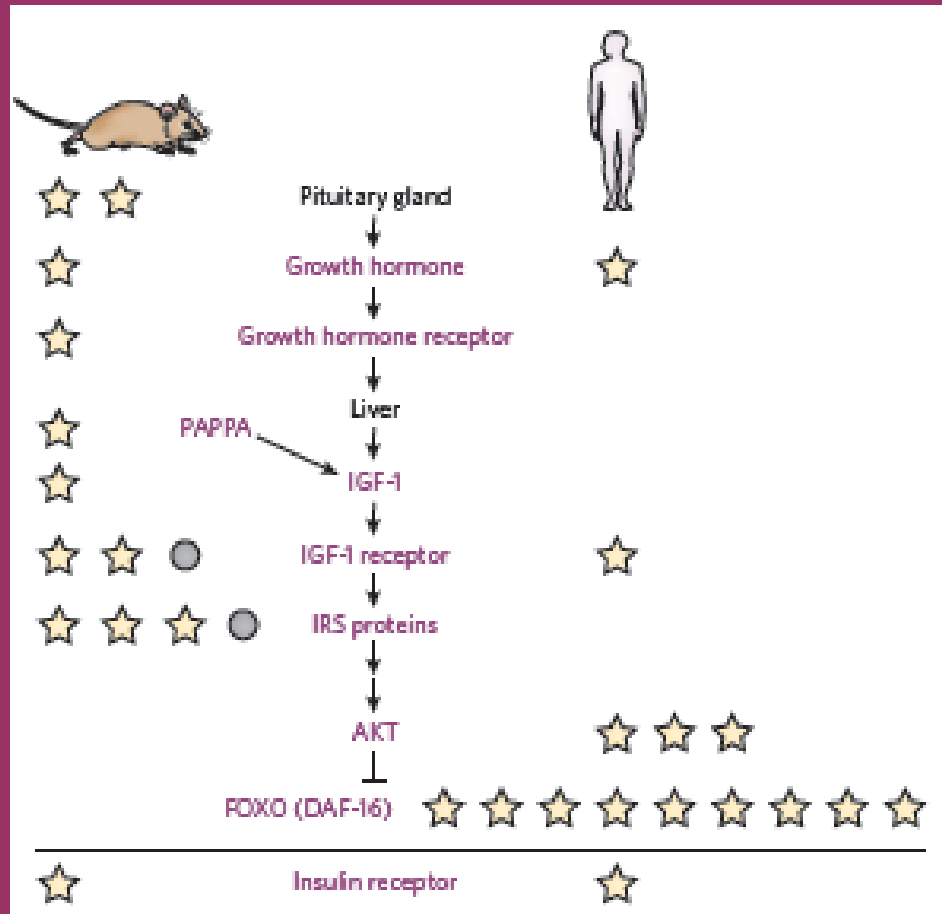
Figure 1. Representation of genetic factors' influence in aging and lifespan. The environmental conditions (stress, pesticides), individual genotype (genomic and mitochondrial DNA) and stochastic factors can induce genetic and epigenetic alterations that cause a decline in somatic stem cell function that can be the origin of metabolic, degenerative diseases, cancer and aging in the individuals.

AGED-RELATED STRESS AND DISEASE
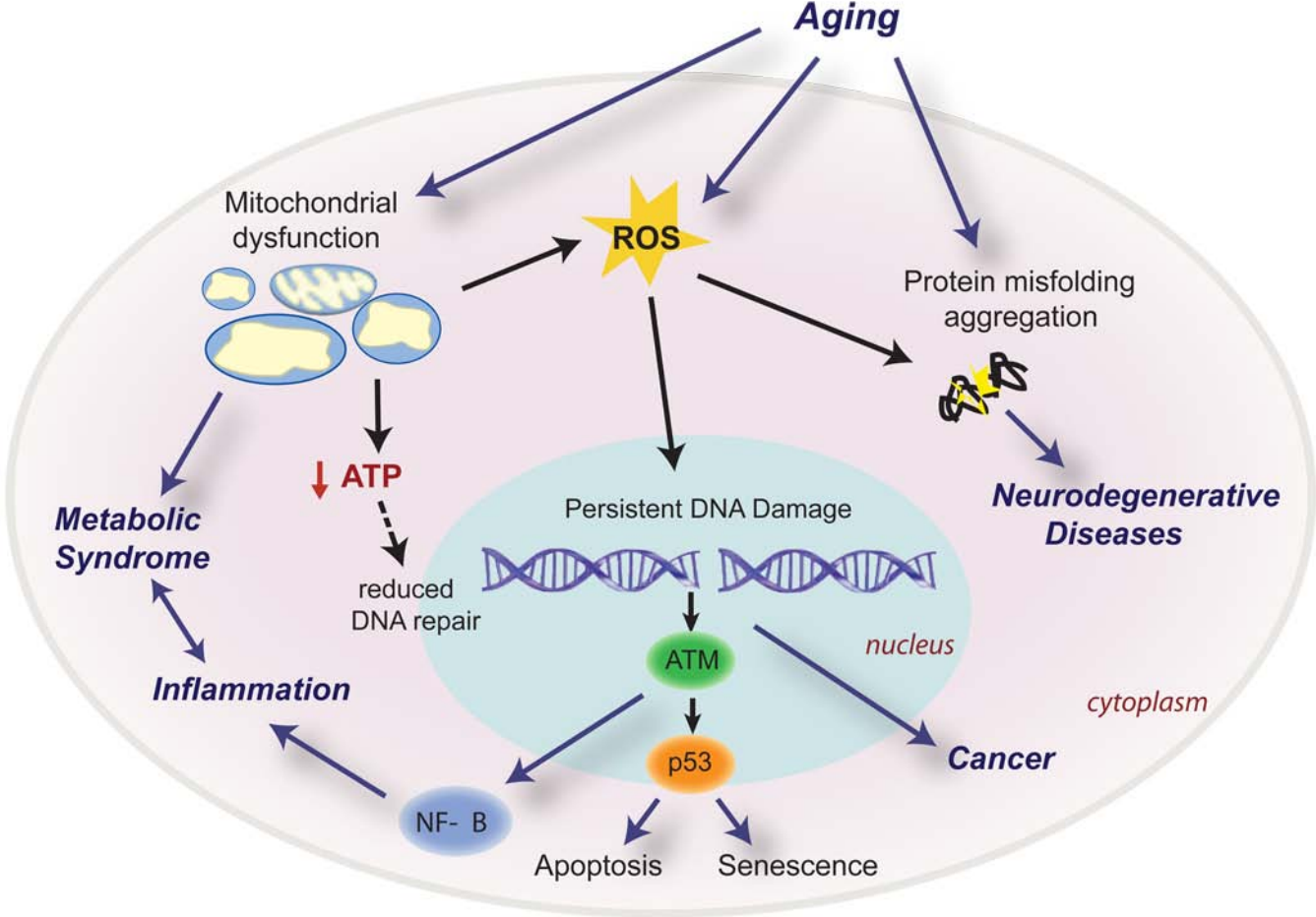
Mitochondrial Biogenesis and healthy Aging

-Mitochondria are particularly susceptive to damage over time as they are the major bioenergetic machinery and source of oxidative stress in cells.

-Effective control of mitochondrial biogenesis and turnover, is critical for the maintenance of energy production, the prevention of endogenous oxidative stress and the promotion of healthy aging.

-Multiple endogenous and exogenous factors regulate mitochondrial biogenesis through the peroxisome proliferator activated receptor gamma coactivator-1α (PGC-1α).

-Activators of PGC-1α include nitric oxide, CREB and AMPK. CR and resveratrol, a proposed CR mimetic, also increase mitochondrial biogenesis through activation of PGC-1α.

PGC-1α regulating network
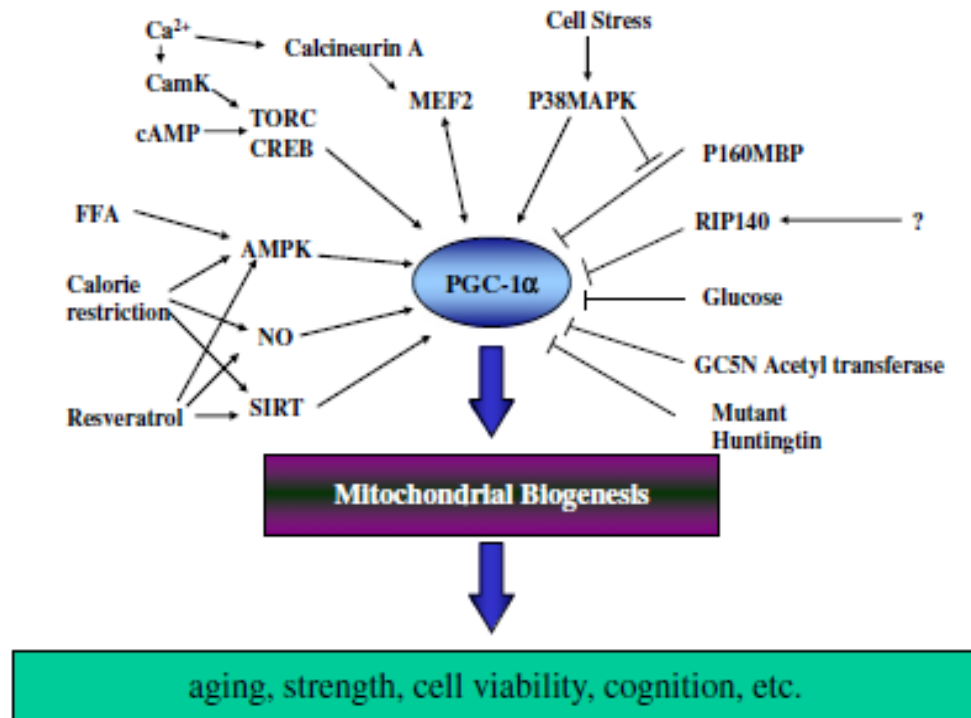
-PGC-1α is at the center of a complex network of signals affected by metabolic, nutritional and environmental factors that modulate (e.g. through transcriptional and post-translational modifications).

AGING and CANCER

-**Same signaling** pathways that are <u>involved in cancer are also involved in cellular and organism aging</u>.

-In **1917** it was shown that CR, a reduction in food intake without malnutrition, <u>extends life span</u> and <u>prevents</u> age related infertility in rodents.

-**Cancer** is not a disease limited to a number of proliferating mutated cells but a **complex process** that also involves interactions with the **neighboring non-mutated mesenchymal and inflammatory cells that are also affected by aging** and/or cancer risk factors.

CANCER

A complex multistage disease associated with accumulation of multiple DNA mutations that cause a deregulation of cell proliferation and differentiation, loss of normal tissue organization, and eventually tissue invasion and dislocation to distant sites.

DNA damage, which occurs continuously in both the dividing and non-dividing cells of the human body, can increase after exposure to exogenous genotoxic carcinogens (e.g. radiations, chemicals, tobacco smoke, viruses, aflatoxin and other food-derived carcinogens), can be prevented or repaired by endogenous protective small molecules and enzymes.

However, detoxification and repair systems might fail, particularly in environments that promote cell proliferation and inhibit cell apoptosis.

Accumulation of multiple DNA mutations in critical genes (i.e. oncogenes or tumor suppressor genes) of particular cells, if not properly controlled through induction of senescence or apoptosis, can lead to uncontrolled cell proliferation and progressive transformation of normal human cells into highly malignant tumor cells.

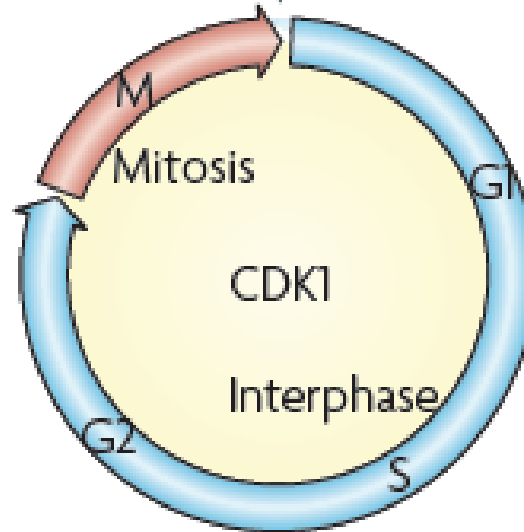# Checkpoint for DNA damage
Role of p53
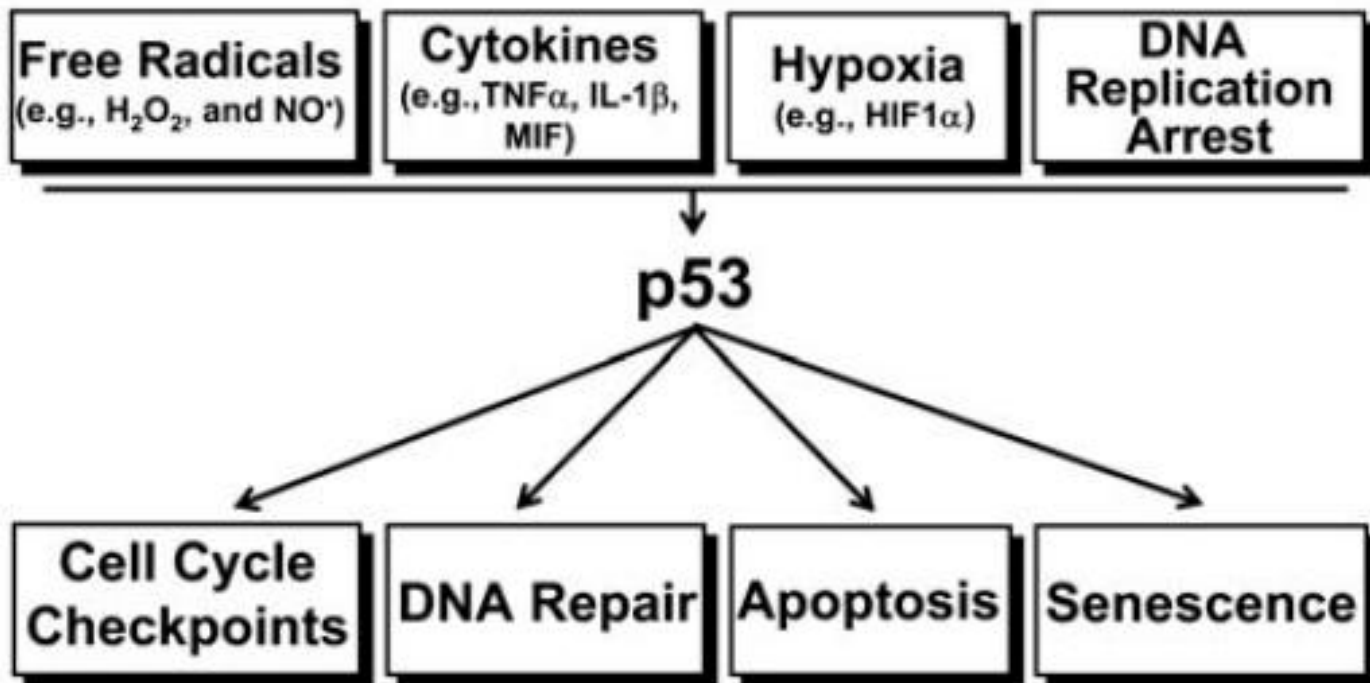
Hallmarks of Cancer
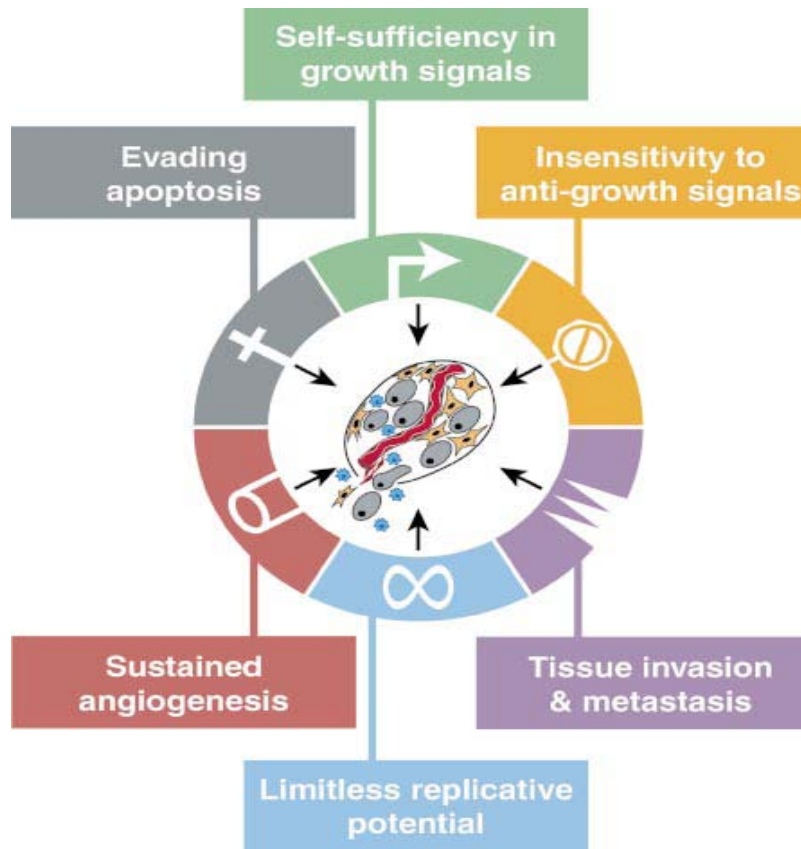
-Initiation
-Promotion
-Progression

-Tumor microenvironment and cell-to-cell interactions between cancer cells and their neighbor stromal and inflammatory cells play a central role in driving tumor cell proliferation, tissue invasion and metastasis.

CANCER

Convergent Mechanisms
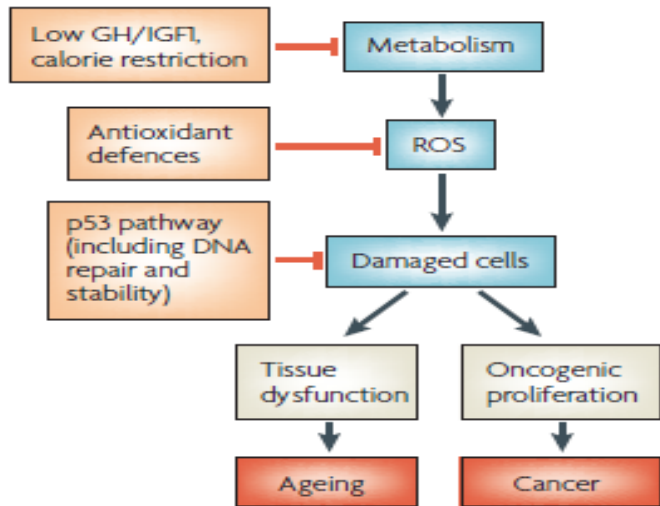
Figure 1 | **Convergent mechanisms of cancer and ageing.** A main source of damage for cells originates from the cellular metabolism through the production of reactive oxygen species (ROS), which ultimately cause macromolecular damage, including DNA damage. This endogenous damage is thought to fuel the process of ageing as well as cancer. Those mechanisms that diminish the generation of endogenous damage, including decreased growth hormone (GH) and insulin-like growth factor-1 (IGF1) signalling, calorie restriction, antioxidant strategies and signalling by the tumour suppressor p53, simultaneously protect cells from ageing and from cancer.

-**Improved Metabolic Efficiency: mitochondrial respiration.**
-**Antioxidant Defenses: reduced ROS production**
-**Tumor Suppressor p53: integrator of cellular stress**
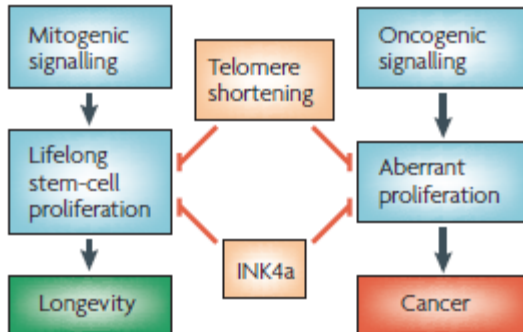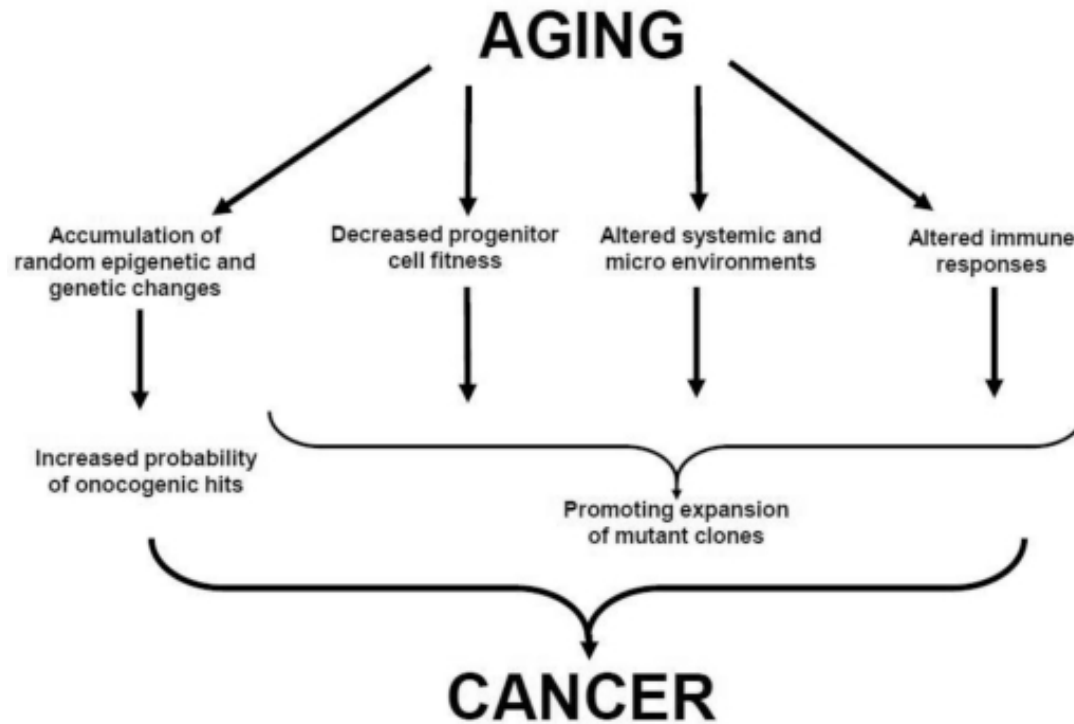
Divergent Mechanisms

Figure 2 | **Divergent mechanisms of cancer and ageing.** Cells possess two main autonomous systems to limit their proliferative potential: telomere shortening and upregulation of the cyclin-dependent kinase inhibitor INK4a. Both systems impact on the proliferative potential of stem cells, particularly at old age, and on the aberrant proliferation stimulated by oncogenic signalling. This limit, while beneficial to prevent the development of cancer, may be detrimental for tissue regeneration at an advanced age and, therefore, may promote ageing.
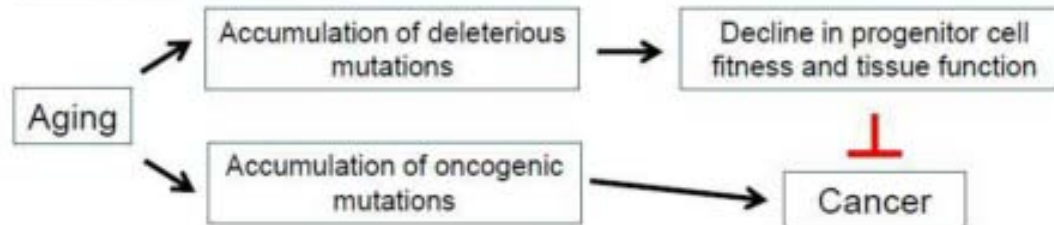
-Telomeres shortening
-p16 ^{INK4a}: binds and inhibits CDK4 and CDK6
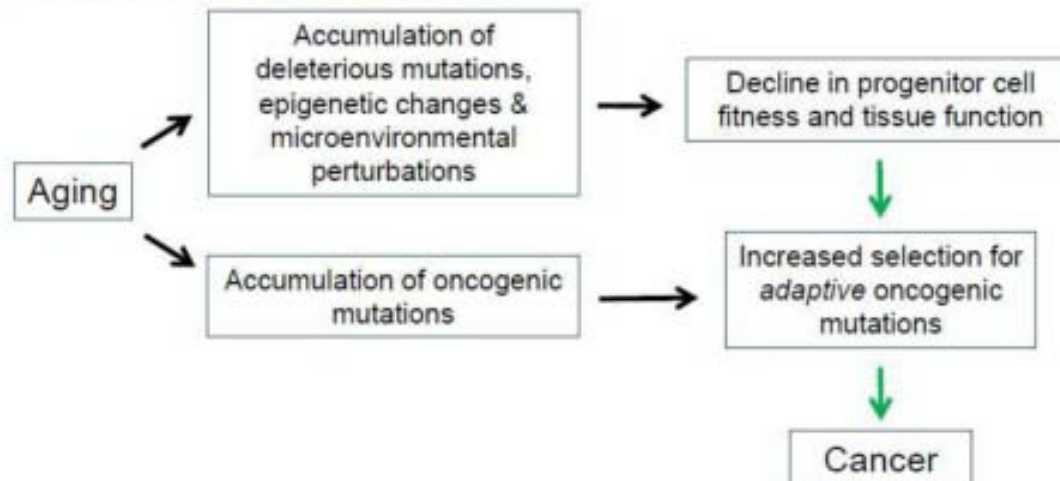
PROPOSED LINKS BETWEEN AGING AND CANCER
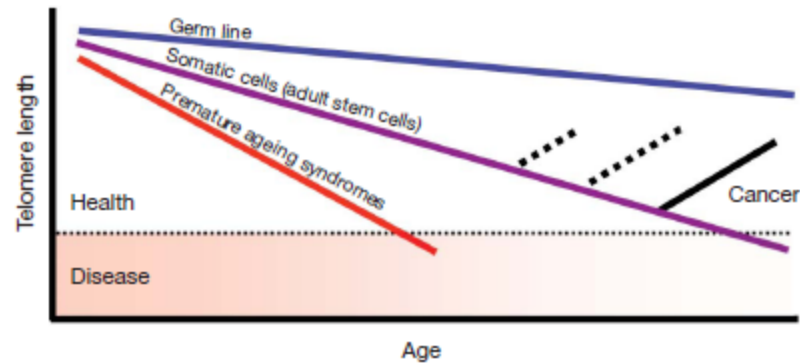
# EMERGING MODELS FOR AGING AND CANCER

A. Predominant Model

Aging

→ Accumulation of deleterious mutations → Decline in progenitor cell fitness and tissue function

→ Accumulation of oncogenic mutations → Cancer

B. Adaptive Oncogenesis Model

Aging

→ Accumulation of deleterious mutations, epigenetic changes & microenvironmental perturbations → Decline in progenitor cell fitness and tissue function

→ Accumulation of oncogenic mutations → Increased selection for *adaptive* oncogenic mutations → Cancer

# Role of telomeres in cancer and aging

Factors that accelerate telomere loss:
Perceived stress
Smoking
Obesity

Premature ageing syndromes:
Ataxia telangiectasia (*ATM*)
Werner syndrome (*WRN*)
Bloom syndrome (*BLM*)
Dyskeratosis congenita (*DKC1*, *TERC*)
Aplastic anaemia (*TERC*, *TERT*)
Fanconi anaemia (Fanc genes)
Nijmegen breakage syndrome (*NBN*)

AGING CONNECTS TELOMERASE WITH MITOCHONDRIAL FUNCTION
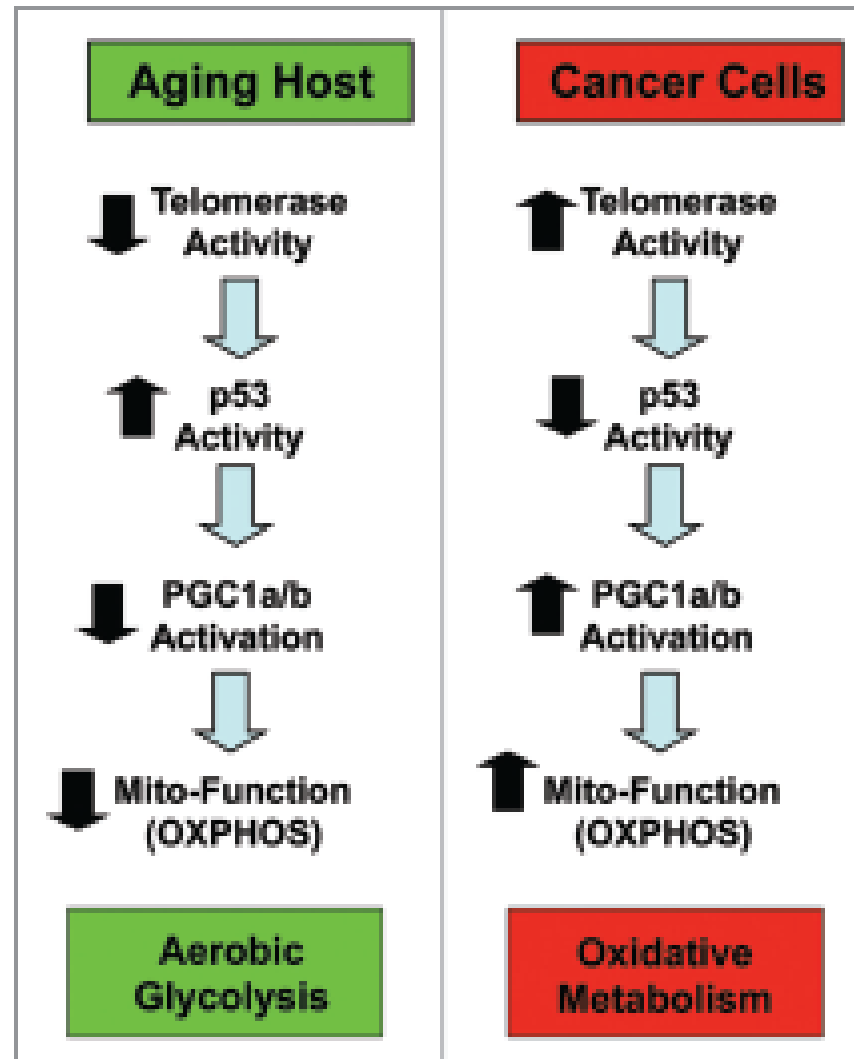
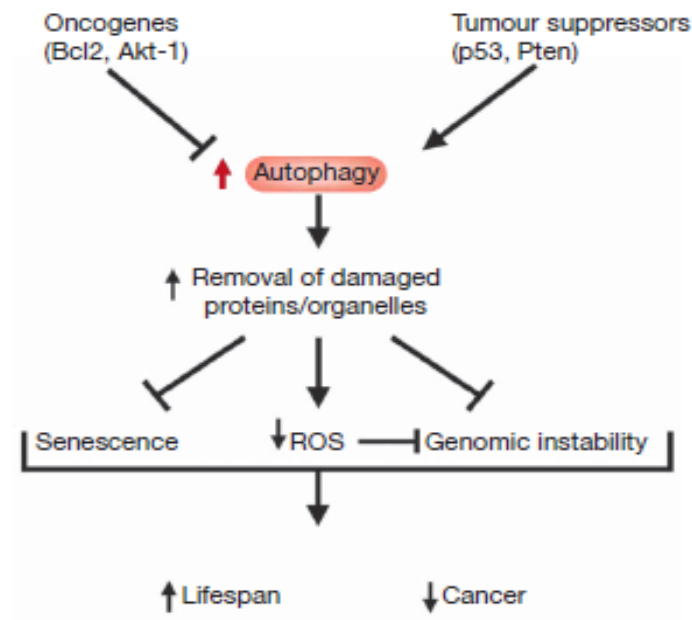# Balance between convergent and divergent mechanisms of cancer and ageing
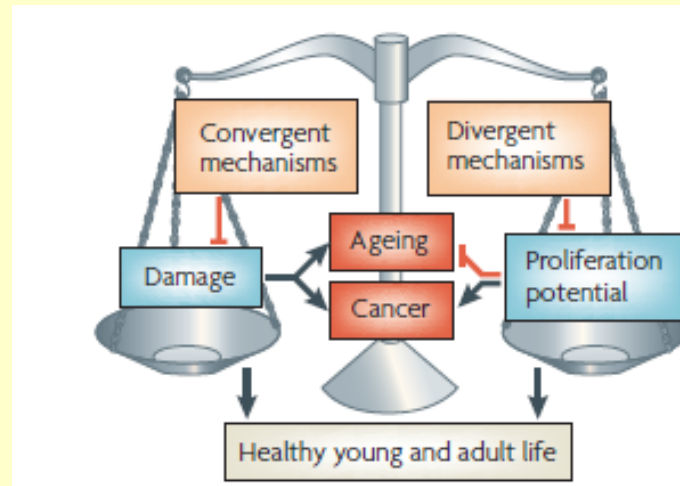
Figure 3 | The potential role of autophagy in cancer and ageing. Autophagy is a regulated process for the removal of damaged proteins and organelles. Autophagy occurs under basal conditions and is stimulated by environmental factors such as starvation. There is evidence that proteins that are linked to tumorigenesis can regulate the rate of autophagy, with oncogenes in general blocking and tumour suppressors stimulating the process. The removal of damaged cellular components, especially damaged mitochondria, might decrease the level of reactive oxygen species (ROS), which in turn might reduce genomic instability or forestall cellular senescence. Such mechanisms might allow moderate increases in autophagy to reduce the incidence of cancer and prolong lifespan.
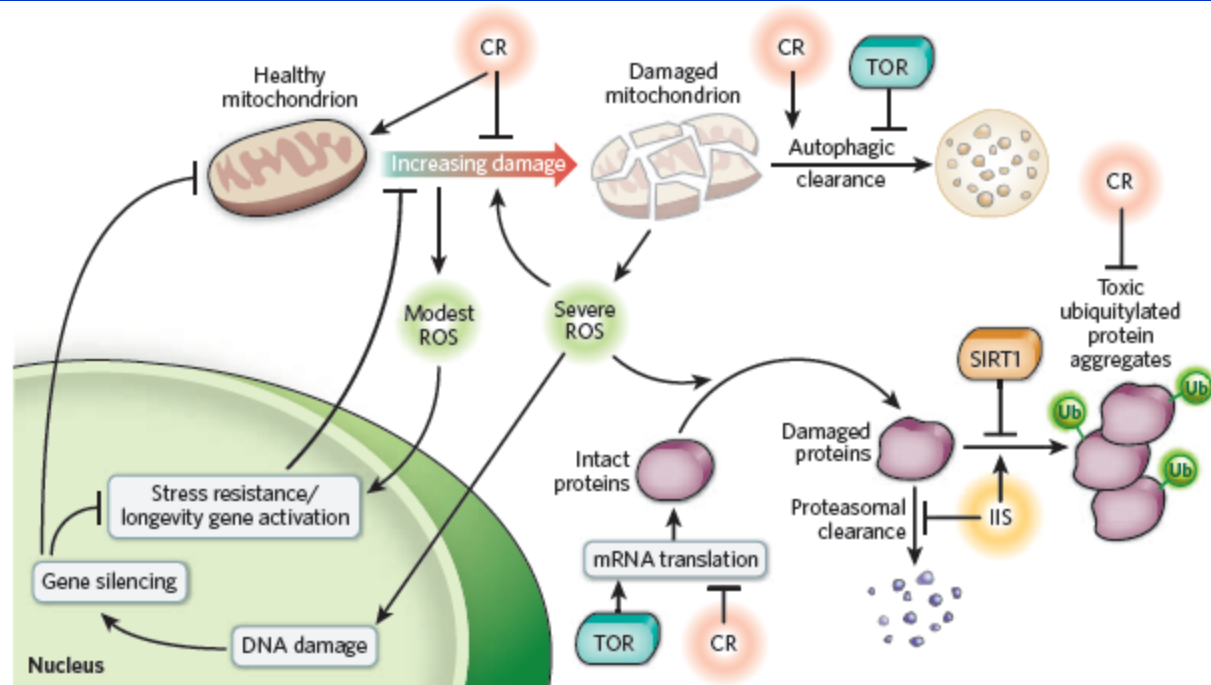
Genotoxic Stress Model of Aging
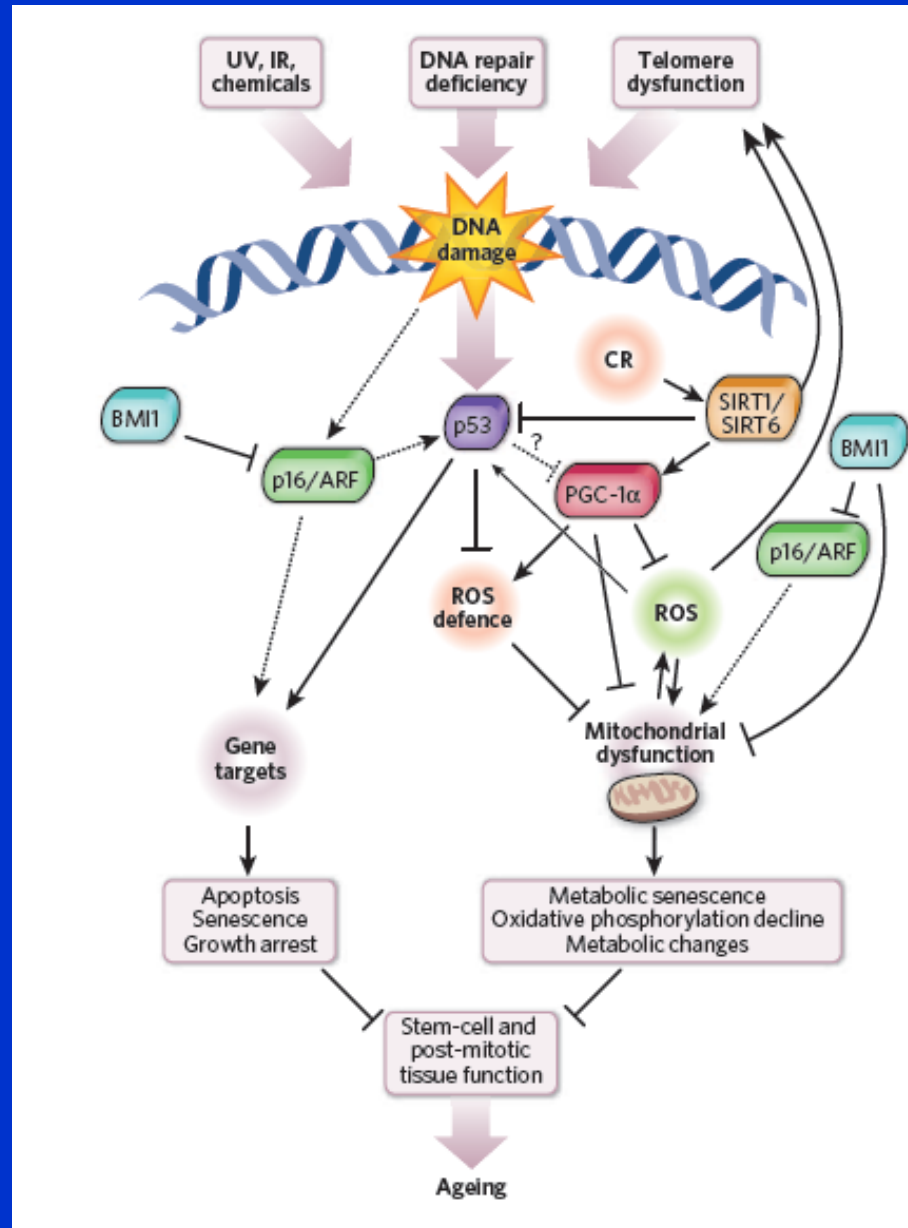
Figure 3 | Conserved pathways that regulate organismal and brain ageing. Shown are mechanisms that involve mitochondrial function, oxidative stress, autophagy, protein homeostasis, TOR signalling, insulin/IGF-1 signalling (IIS), caloric restriction (CR) and sirtuins. Modest concentrations of ROS generated by mitochondria during normal metabolism may induce stress-resistance pathways that scavenge ROS and repair damage. However, progressive mitochondrial damage may lead to pathological concentrations of ROS production, which, in turn, may contribute to further mitochondrial damage. Damaged mitochondria can be cleared by autophagy, which is promoted by CR and inhibited by TOR signalling. CR improves overall mitochondrial function, in part, by promoting mitochondrial biogenesis and reducing ROS production[100].

ROS can damage other crucial macromolecules, such as DNA and proteins. Unrepaired DNA damage may give rise to epigenetic changes and gene silencing and may exacerbate mitochondrial impairment by reducing the expression of nuclear-encoded mitochondrial genes. ROS can also modify proteins, leading to protein unfolding and aggregation. Modified proteins can be removed by a number of degradative pathways, including the ubiquitin–proteasome pathway. Inadequate clearance may lead to the accumulation of toxic protein aggregates. The dynamics of protein clearance and aggregate formation may be modulated by the IIS pathway and by SIRT1 and CR. The accumulation of damaged and toxic proteins may also be modified through the regulation of messenger RNA translation by TOR signalling and CR.
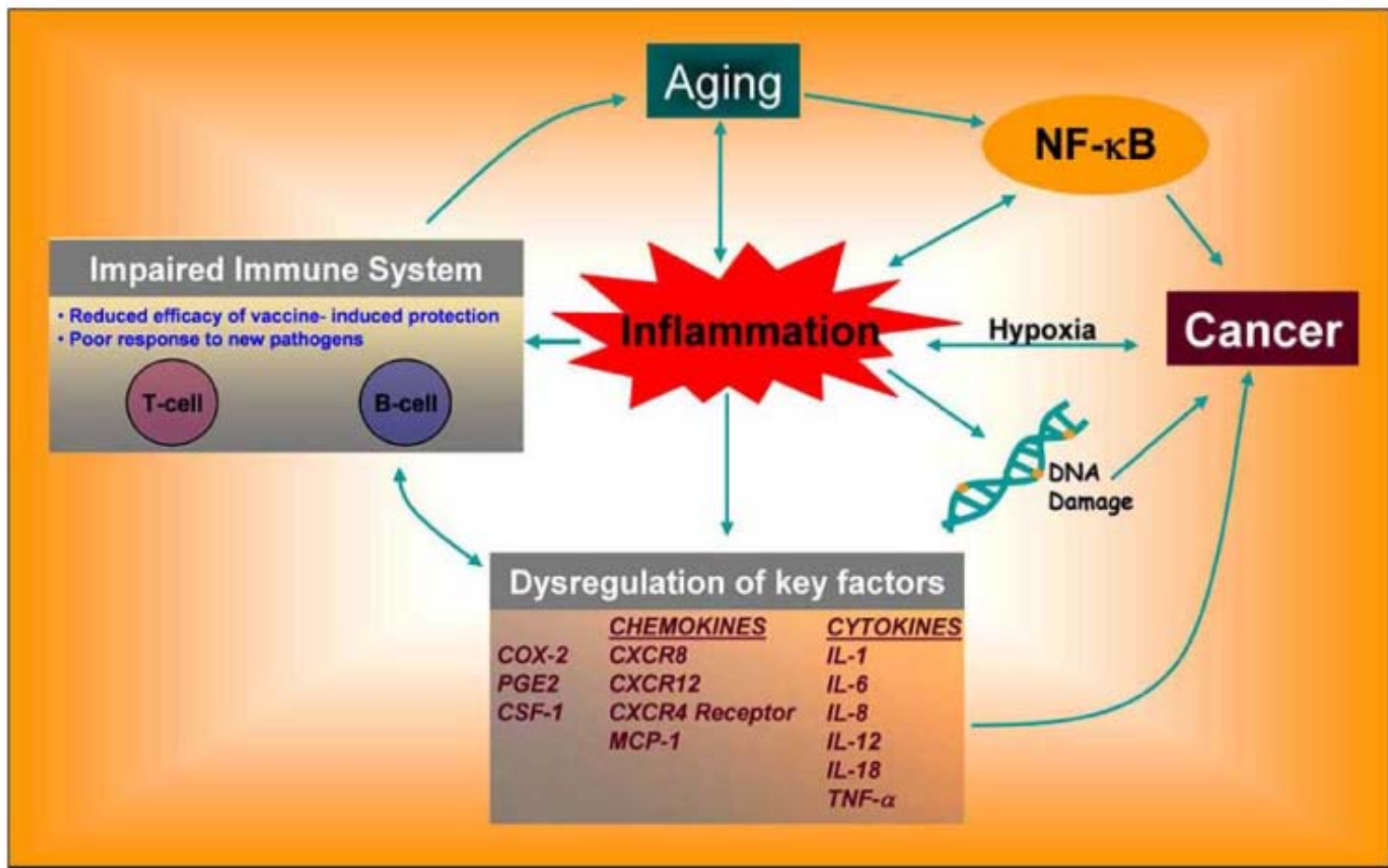
Fig. (1). Schematic representation of various biochemical events that connect the processes of aging and cancer

Inflammation is an important factor involved in the induction of aging as well as chronic diseases, including cancer. Interestingly, inflammation is also observed as a consequence of these processes. NF-kB is well-known to be involved in the process of cancer development; emerging data suggests its involvement in the aging process as well.

The role of SIRT1 in the induction of age-associated physiological changes

TRENDS in Pharmacological Sciences
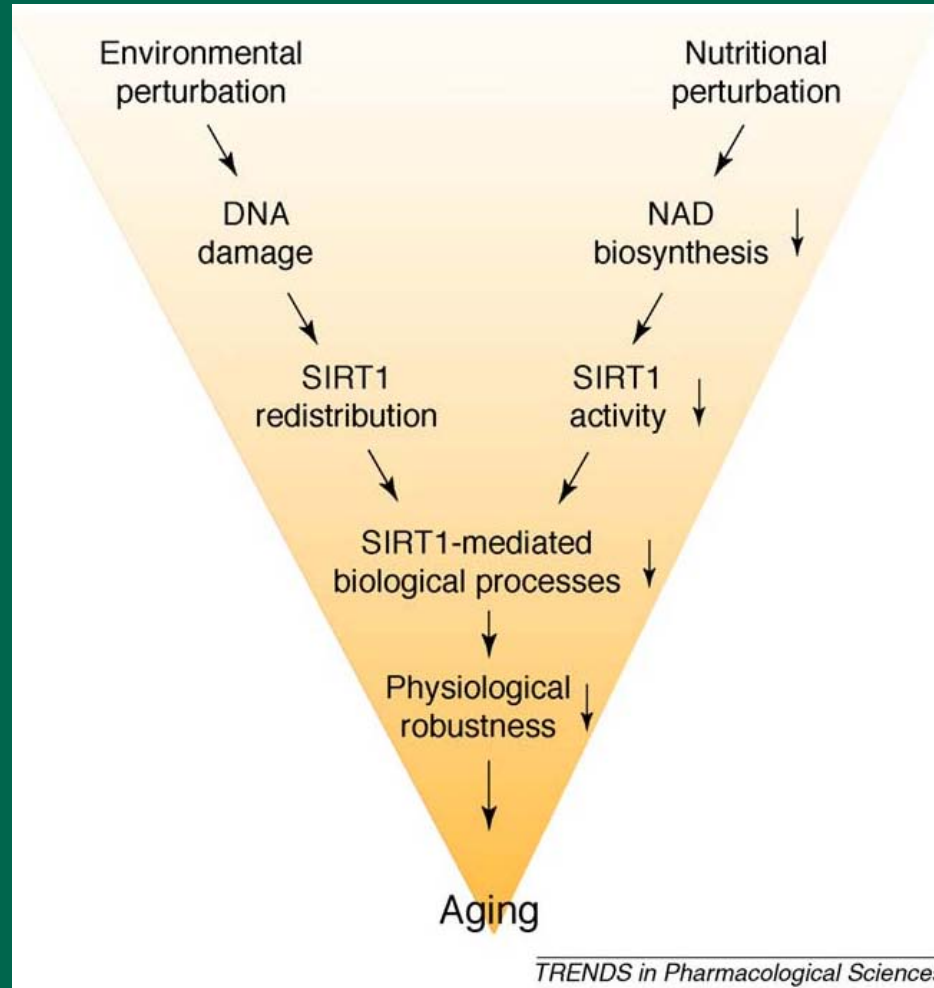
Sirtuin is a nicotinamide adenine dinucleotide (NAD^+)-dependent deacetylase.

Figure 1. Representation of the possible connections of stemness, aging and cancer processes, mediated by SirT1. For each process, the two main effects in which SirT1 has been implicated are indicated in the external circle.

SIRT1: a molecular target for pharmaceutical and nutriceutical anti-aging interventions.

TRENDS in Pharmacological Sciences
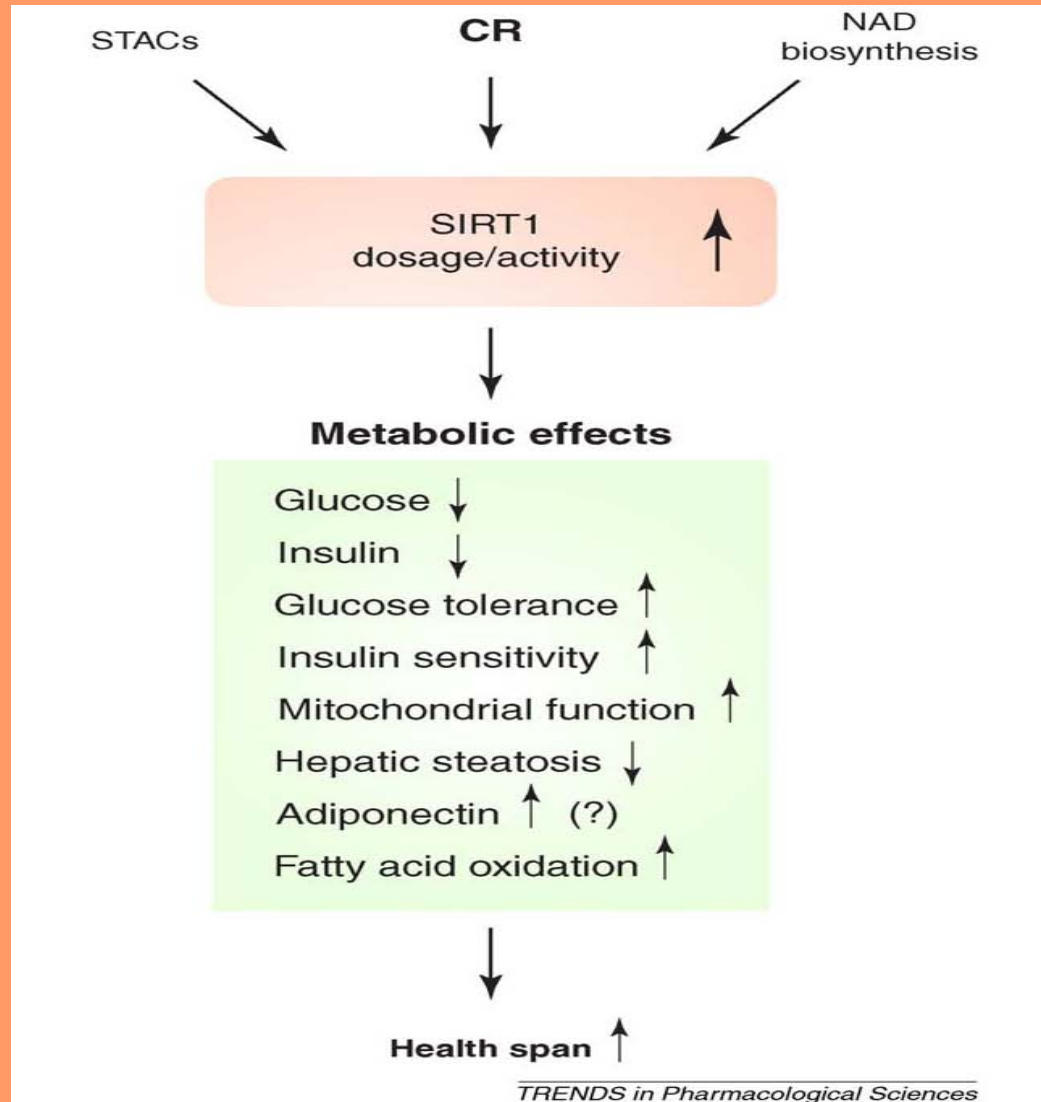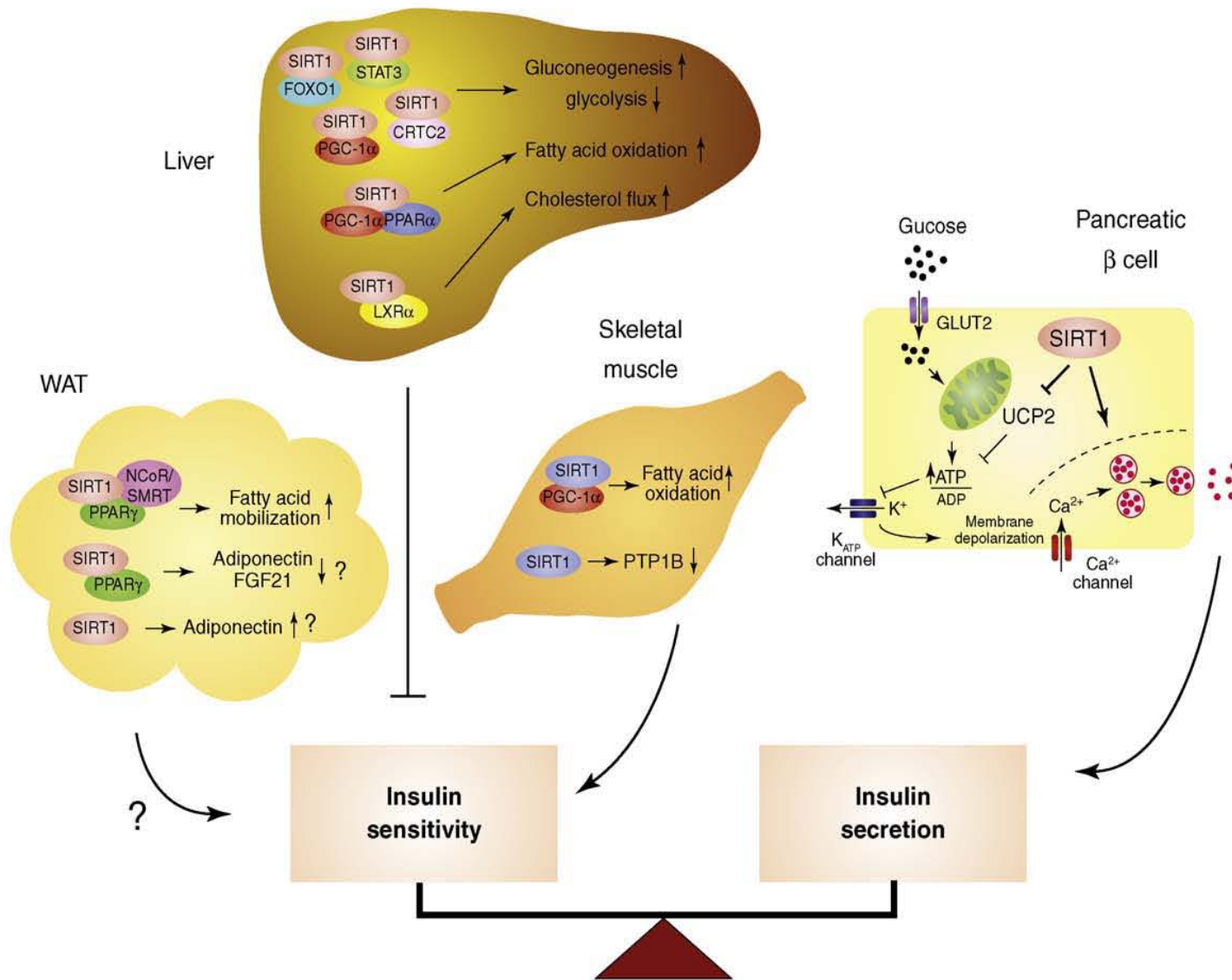
Tissue-specific metabolic functions of SIRT1 in the regulation of the sensitivity and secretion of insulin.

CR and Cancer

CR without malnutrition is the most ==potent== and reproducible physiological intervention for increasing lifespan and protecting against cancer in mammals.
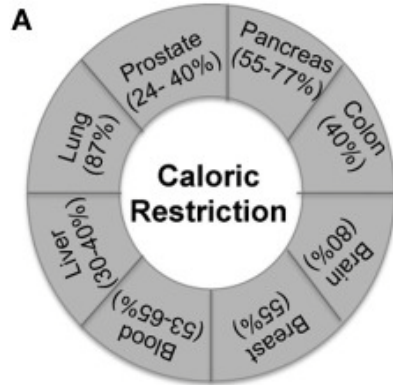
==CR reduces== the levels of <u>several anabolic hormones</u>, growth factors and inflammatory cytokines, reduces oxidative stress and cell proliferation, <u>enhances</u> <u>autophagy</u> and several <u>DNA repair processes</u>.

==<u>Nutrition:</u>== diet (fried, red meat, preserved food, alcohol, salted, vitamins, nutrients) <u>plays an important role</u> in <u>initiation, promotion and progression</u> in cancers in Western countries.

==<u>Excessive adiposity and cancer risk</u>==: chronic inflammation, adiponectin, leptin and cytokines.
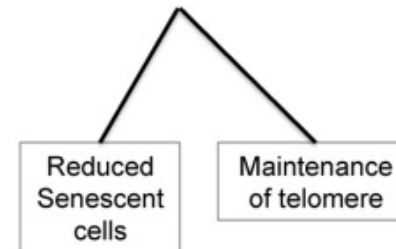
<u>Endocrine regulation by insulin and steroids</u>.

CALORIC RESTRICTION AND CANCER

A

Prostate (24- 40%)
Pancreas (55-77%)
Lung (87%)
Colon (40%)
Liver (30-40%)
Brain (80%)
Blood (53-65%)
Breast (55%)

Caloric Restriction

B

% Tumor Incidences

0 % CR
10 % CR
20 % CR
30 % CR

0% CR
25% CR
40 % CR

Azoxymethane-inJuced colon tumor incidence in male F344 rats fed (Kumar et al., 1990)

DMBA-induced mammary tumors female Sprague-Dawley rats (Ruggeri et al., 1989)
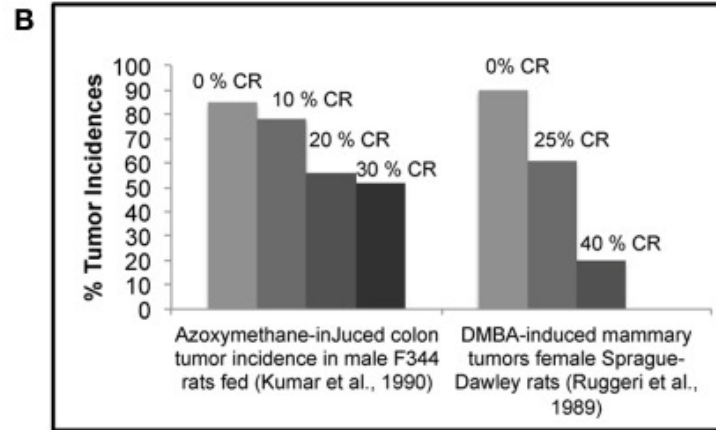
C

Anti- aging and anti- tumorigenic caloric restriction effects

Regulation of ROS level

Regulation of IGF1 level

Inhibition of PI3K-AKT pathway
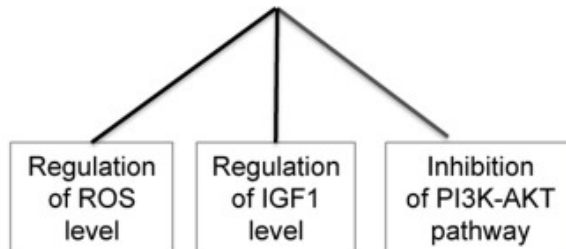
Anti- aging but tumorigenic caloric restriction effects

Reduced Senescent cells

Maintenance of telomere
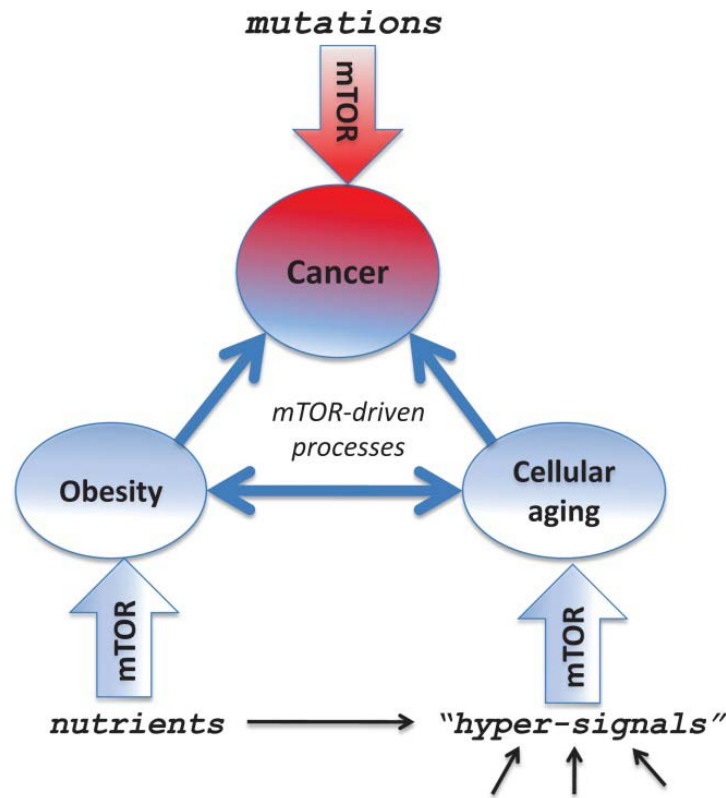
Figure 2: Several mTOR-dependent processes acting in concert can promote cancer. The mTOR pathway is involved in cellular and organismal aging, thus connecting aging to age-related diseases such as cancer. Pro-aging, growth-promoting and inflammatory pathways such as mTOR drive aging and cancer. Rapamycin may decrease cancer by (a) slowing aging, (b) preventing obesity and (c) directly affecting cancer cells.
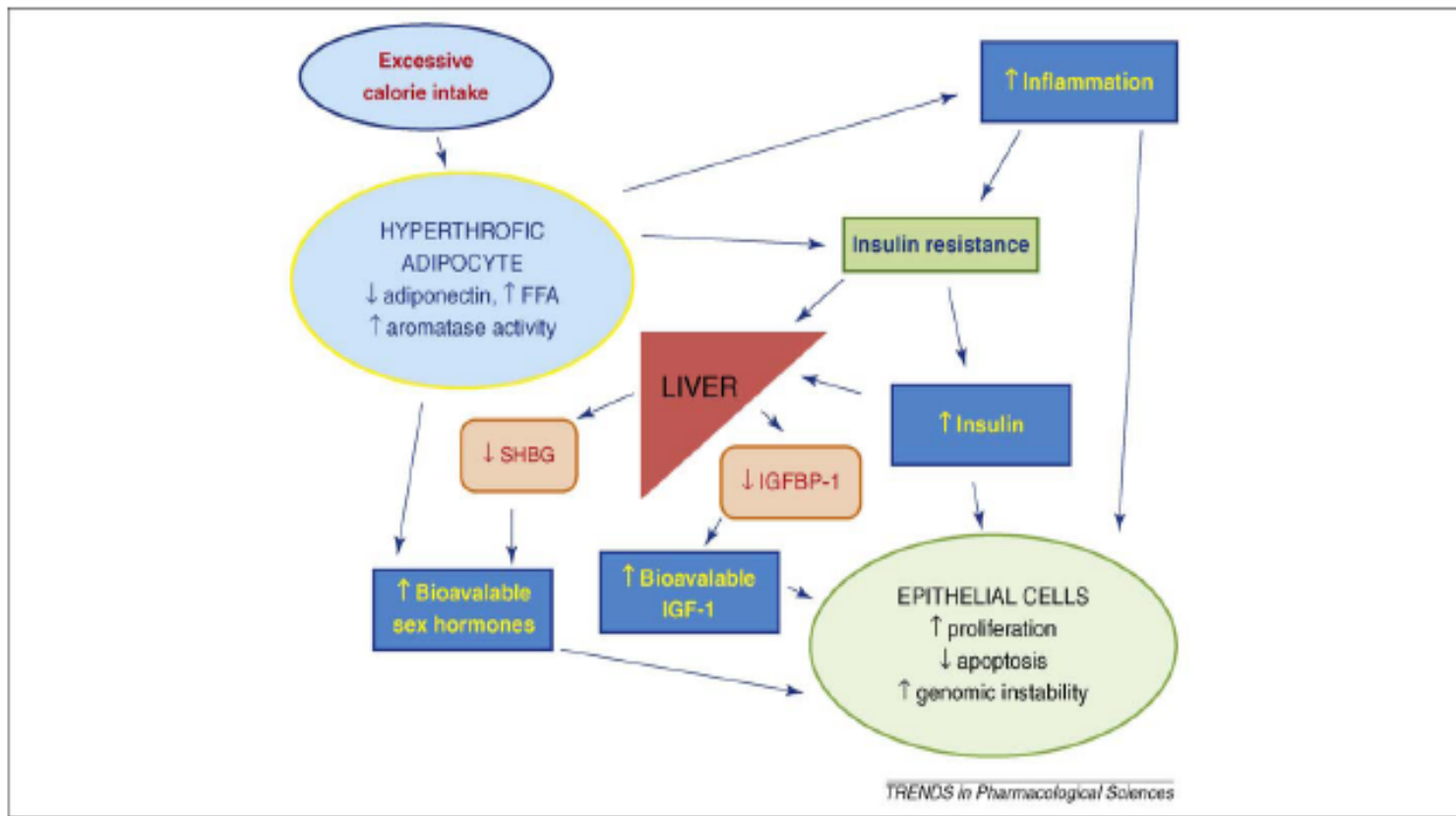
Figure 1. Effects of excessive calorie intake and adiposity on hormones and growth factor production and cell proliferation. Excessive calorie intake and a sedentary lifestyle promote hypertrophy of adipose tissue, reduce adiponectin production and increase circulating free fatty acids (FFAs) and inflammation, leading to insulin resistance and compensatory hyperinsulinemia. Increased serum insulin concentration causes a reduction in hepatic synthesis of IGFBP1 and SHBG that leads to increased bioavailability of IGF-1 and sex hormones. Adipose tissue is also a major source of extraglandular estrogens. Chronically elevated circulating levels of insulin, IGF-1, sex hormones and inflammatory cytokines promote cellular proliferation, genomic instability and inhibit apoptosis in many cell types.

CR and Cancer Prevention
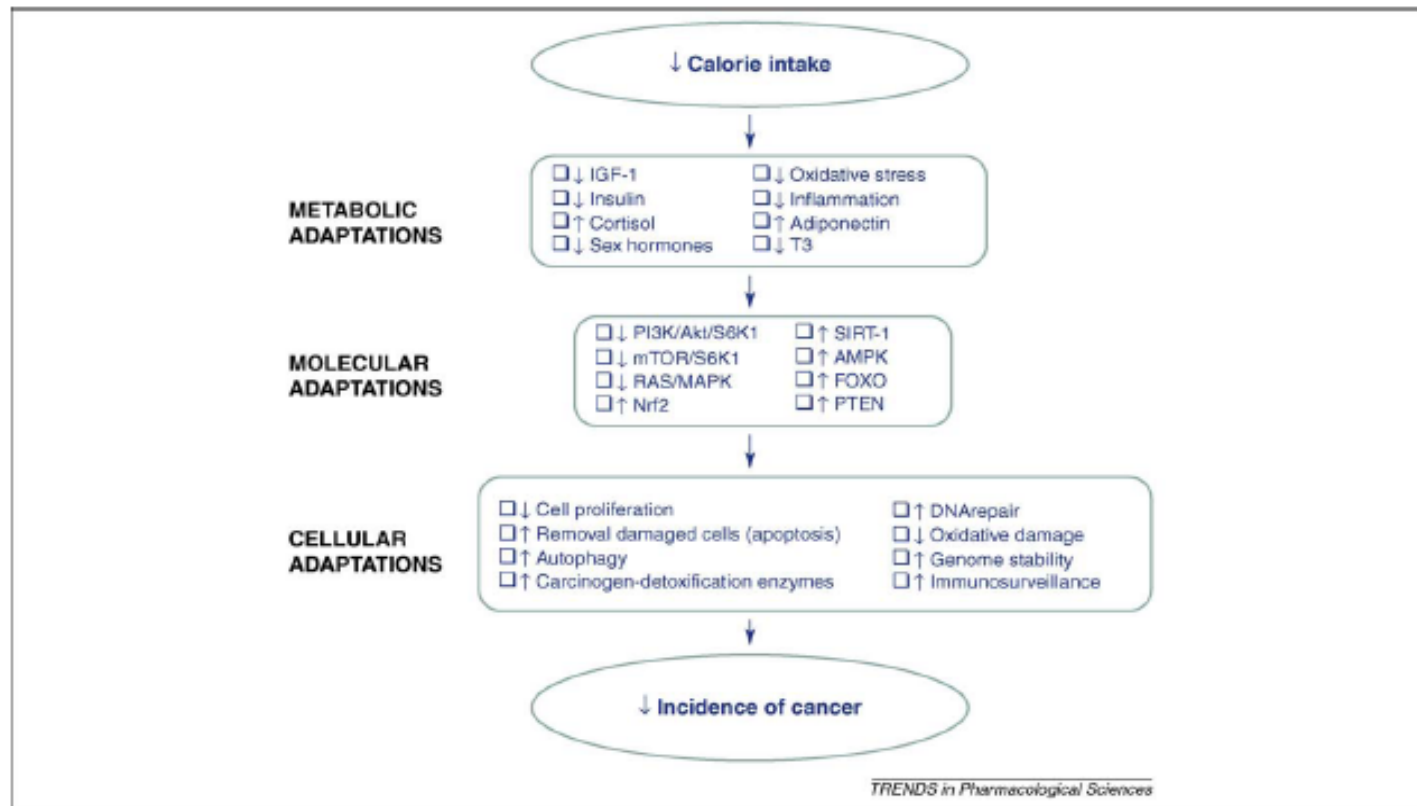
Figure 2. Mechanisms for cancer prevention by CR. CR causes several key metabolic/hormonal adaptations that alter the expression of several genes and signaling pathways (upregulation of certain genes/signaling pathways and downregulation of others as indicated by the arrows), which produce major cellular adaptations (e.g. a reduction in cell proliferation, increased removal of damaged organelles or cells via autophagy or apoptosis, upregulation of DNA repair systems and genomic stability) that result in a reduced cancer incidence (see the text). T3 = triiodothyronine; PI3K = phosphatidylinositol-3 kinase; AKT = kinase AKT, also known as protein kinase B; S6K1 = ribosomal S6 protein kinase 1; mTOR = mammalian target of rapamycin; MAPK = mitogen-activated protein kinase; NRF2 = transcription factors NF-E2-related factor 2; SIRT-1 = silent mating type information regulation 2 homolog 1; AMPK = adenosine monophosphate (AMP)-activated protein kinase; FOXO = Forkhead transcription factors; PTEN = phosphatase and tensin homolog.
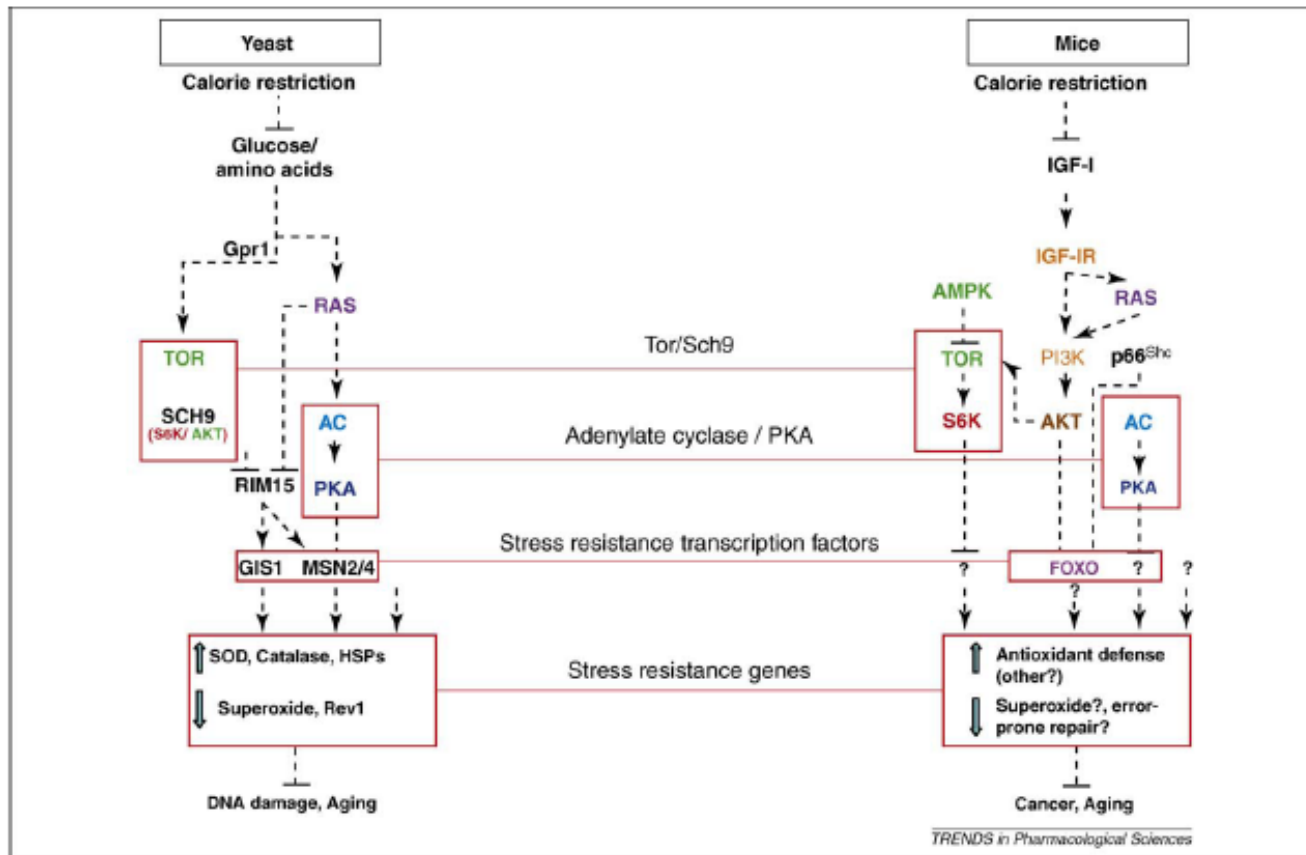
Figure 3. Pro-aging and pro-cancer pathways in yeast and mice. Similar pathways, including Ras, Tor, S6 kinase (S6K), adenylate cyclase (AC) and PKA, have been shown to promote aging in both yeast and mice. In yeast, CR causes the downregulation of these proteins, which promote DNA mutations by reducing the activity of stress resistance transcription factors including Msn2/4 and Gis1 and subsequently increasing the level of superoxide and the activity of error-prone polymerases (Rev1, etc.). In yeast, this DNA damage-promoting mode can occur largely independently of cell division. In mice, orthologs of yeast Tor, S6K, AC and PKA promote aging but are also components of some of the most common oncogenic pathways. CR reduces IGF-I and consequently can reduce the activity of protein functioning downstream of IGF-IR including Tor and S6K. Activation of Tor and S6K but also of AC and PKA might promote DNA damage and cancer in part by promoting cell growth and inhibiting apoptosis in damaged cells and in part by promoting aging and genomic instability independently of the rate of cell growth. These pathways might also contribute to cancer and metastases by affecting inflammation and the cellular environment of the malignant and pre-cancerous cells. The mechanisms connecting IGF-I signaling pathways and cancer in mammals are poorly understood but might involve mechanisms similar to those identified in yeast [147].

CALORIC RESTRICTION

-Reduces activity of pro-aging pathways.

-Reduces growth and inflammation in the pre-cancerous and normal neighbor cells.

-Increases apoptosis in damaged cells might reduce oncogene mutation frequency.

-Modulates the growth and invasiveness potentials of the mutated cancerous cells.

-CR Mimetic:
A. Resveratrol (activates SIRT1) anticancer activity through p53.
B. Metformin: activates genes that reduce glucose production in liver.
C. 2-deoxy-D-glucose: inhibits glycolysis

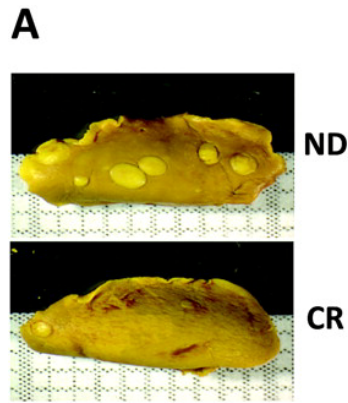# MAJOR METABOLIC PATHAYS THAT REGULATE MAMMALIAN LONGEVITY
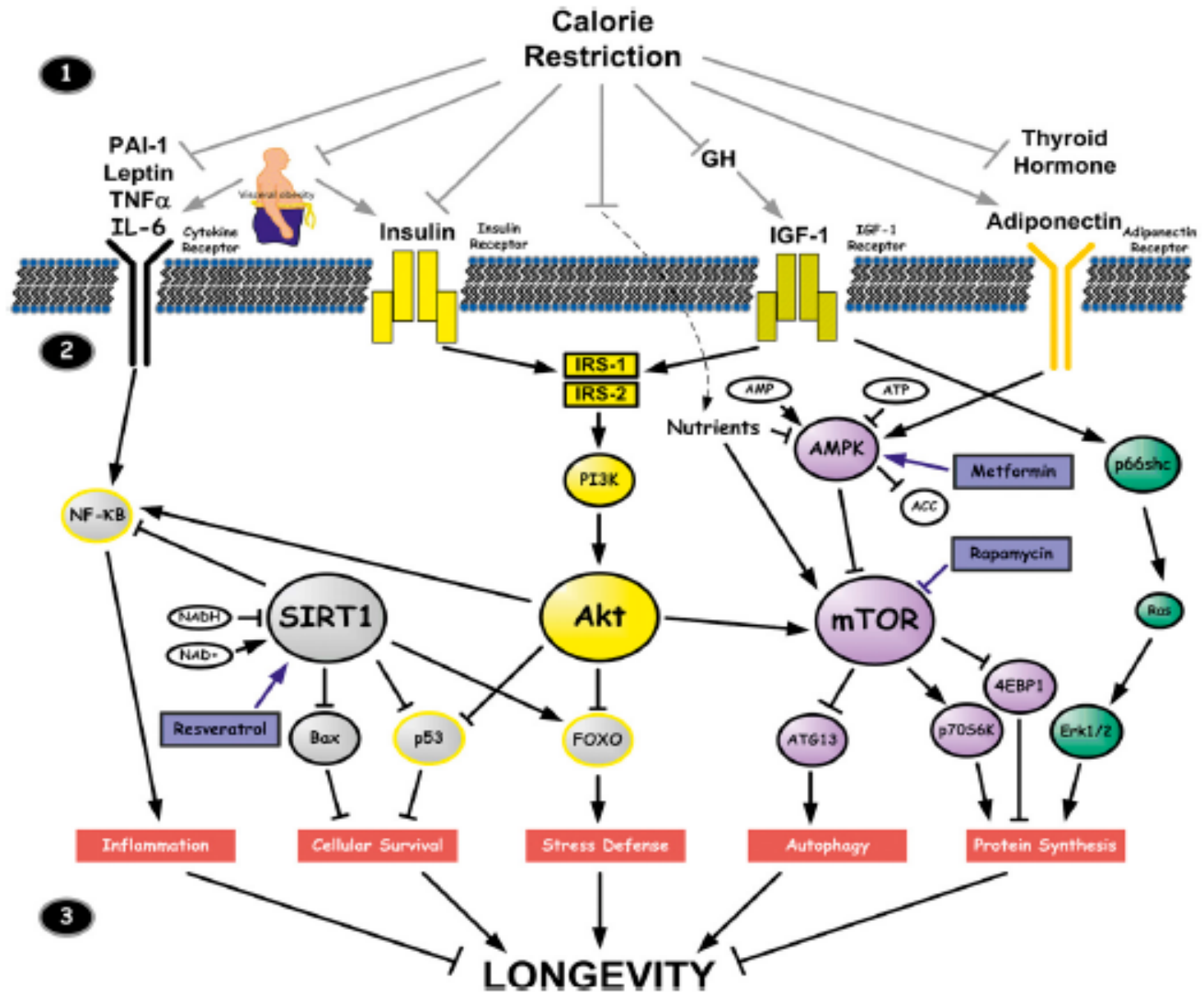
CR causes a significant inhibition of 4T1 murine mammary tumor formation in syngeneic mice.
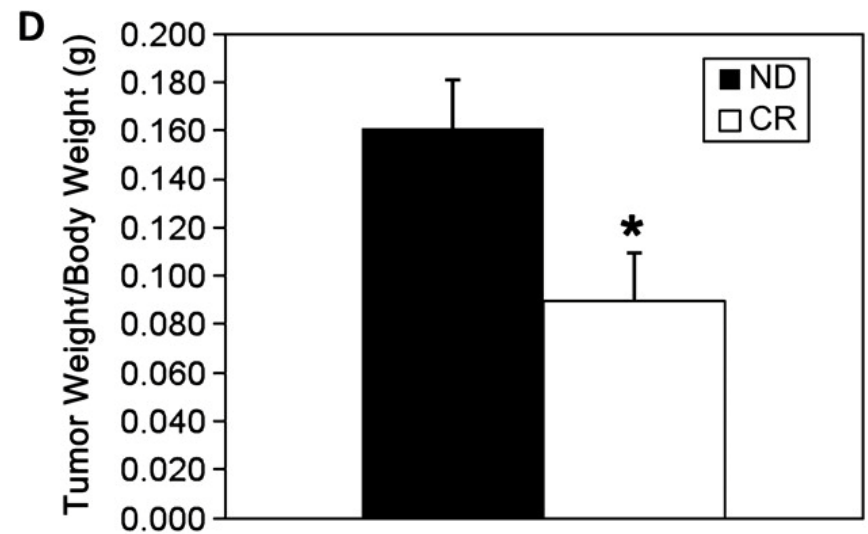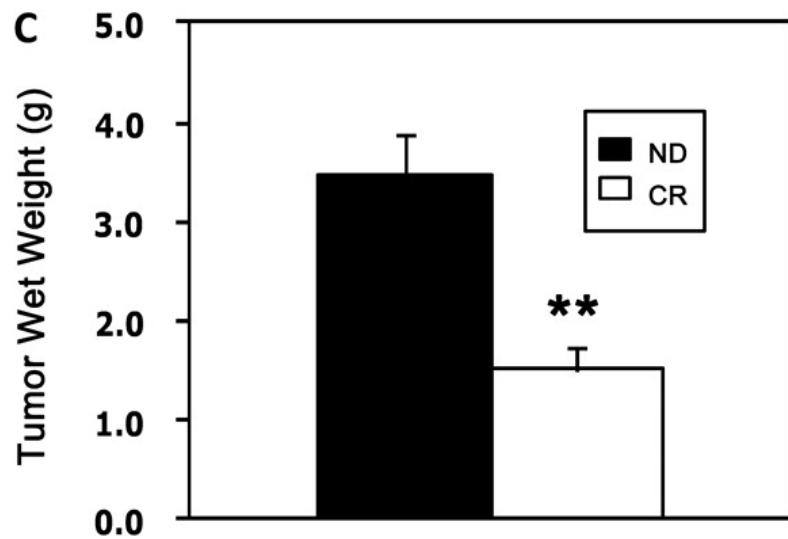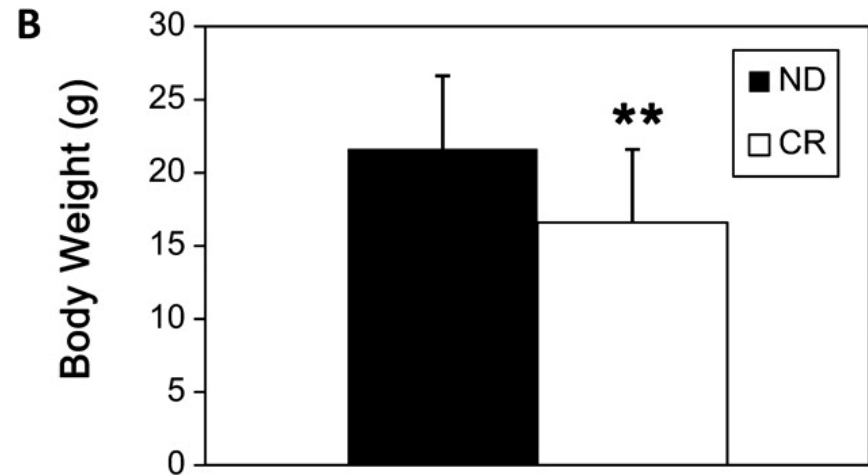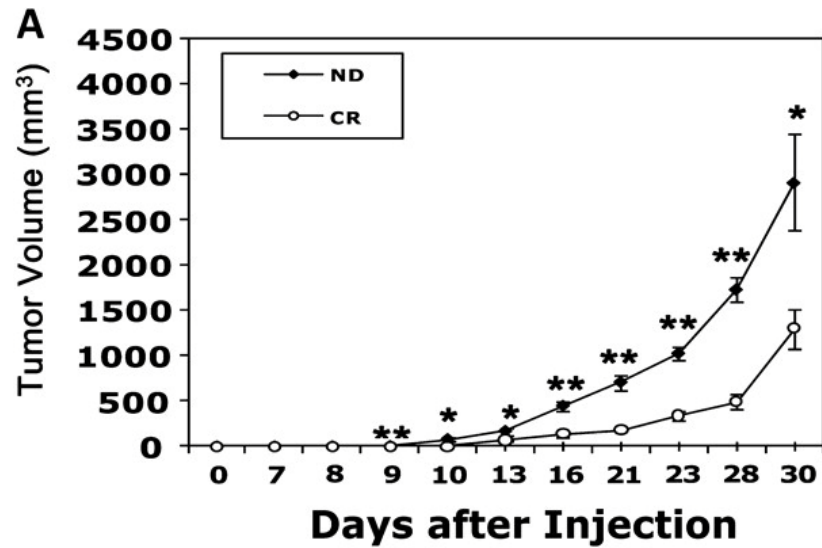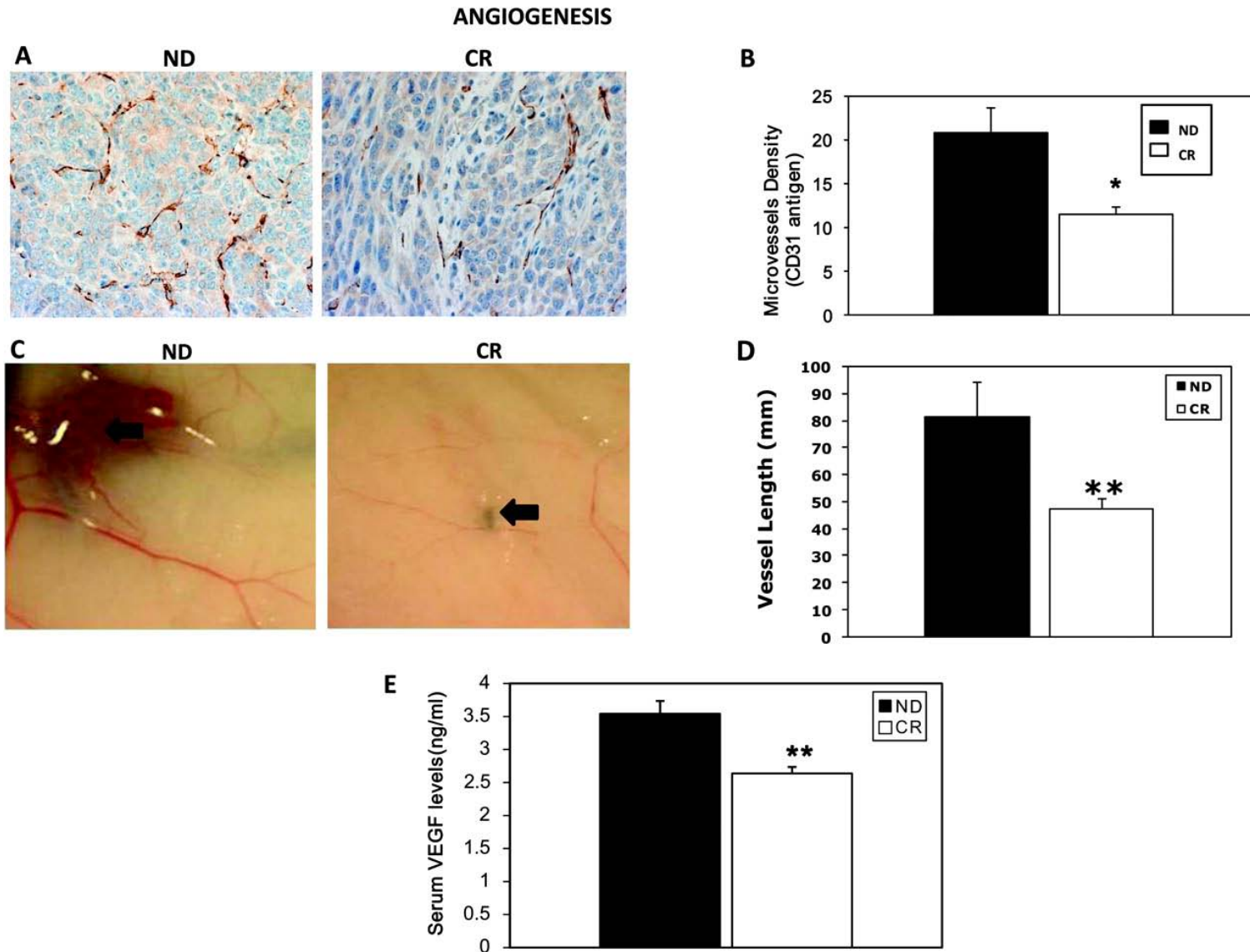

De Lorenzo M S et al. Carcinogenesis 2011;32:1381-1387

Carcinogenesis

CR causes a decrease in the number of spontaneous and experimental lung metastases.
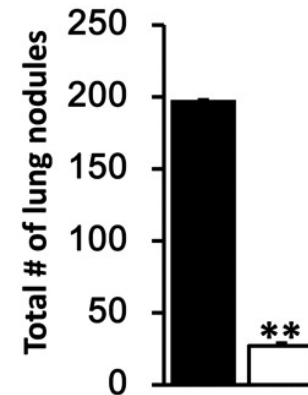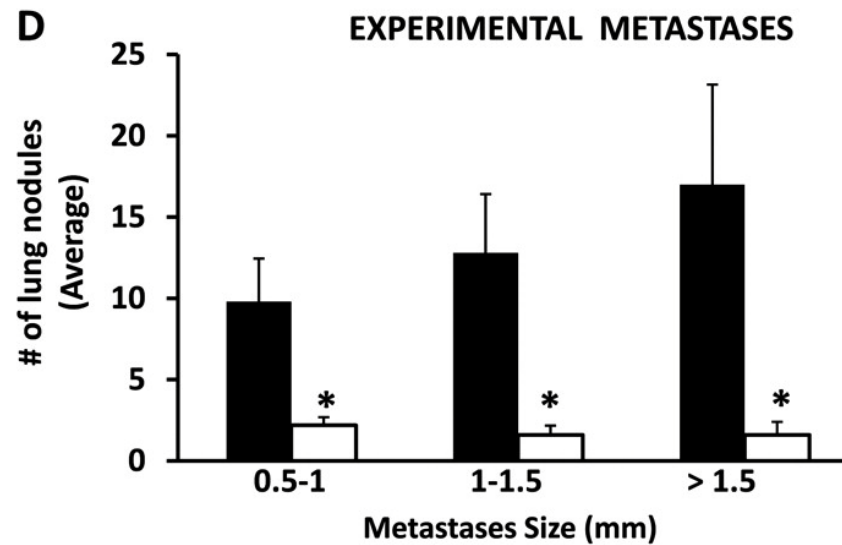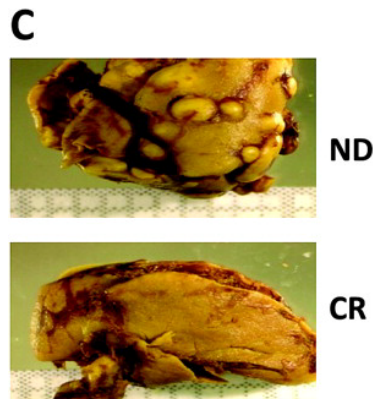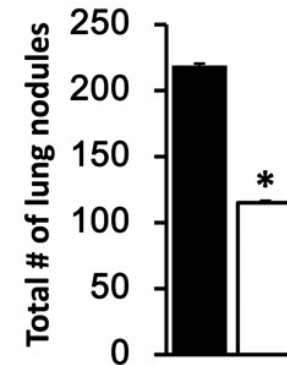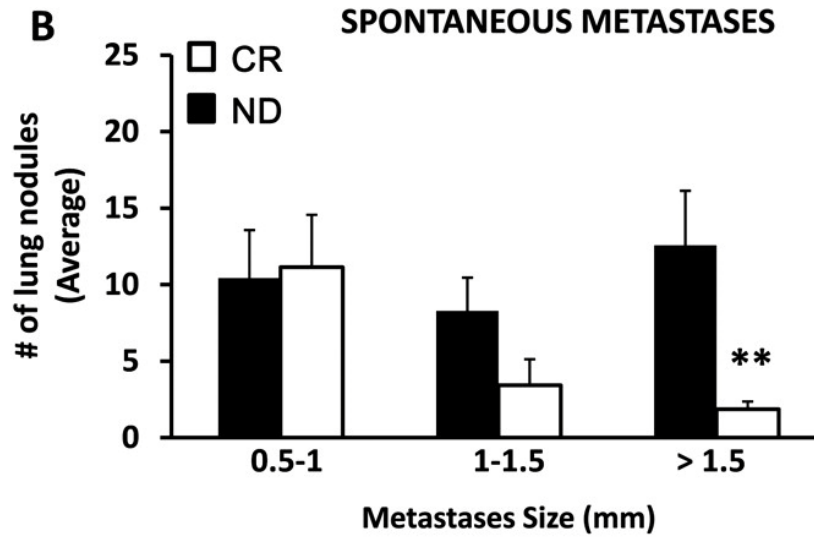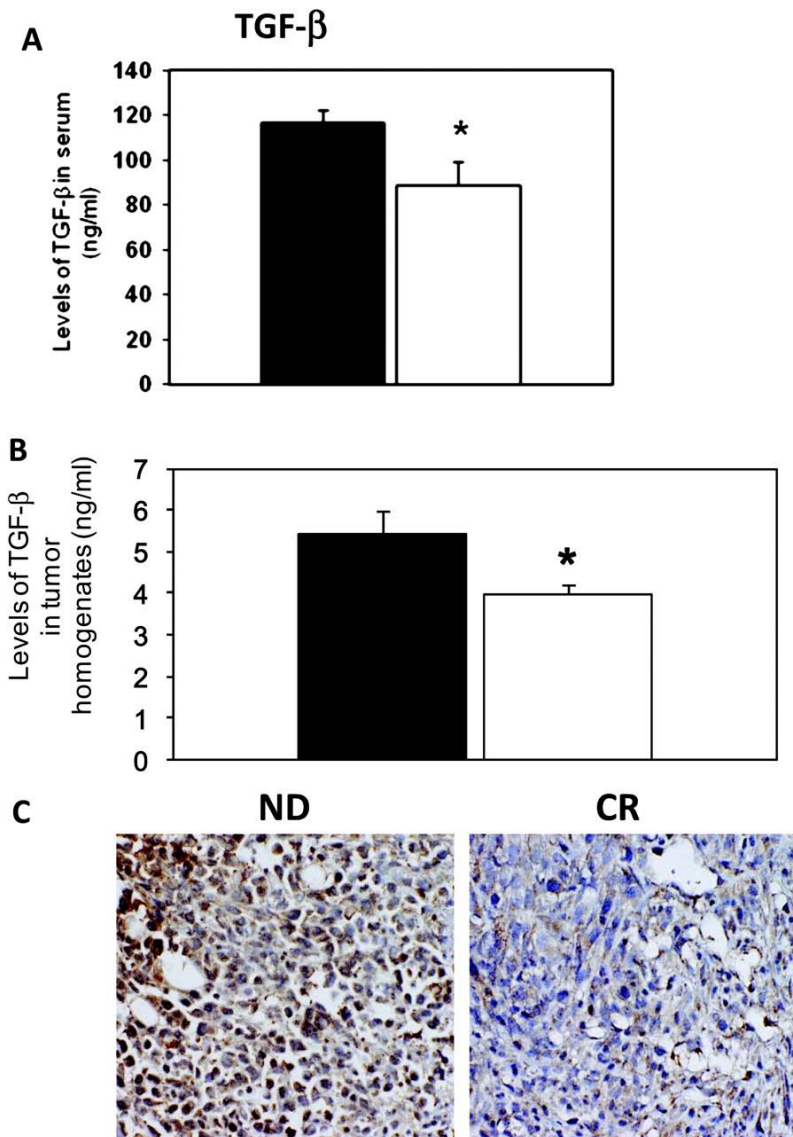

De Lorenzo M S et al. Carcinogenesis 2011;32:1381-1387

Carcinogenesis

CR reduces intratumor microvessel density and in vivo angiogenesis induced by 4T1 tumors.
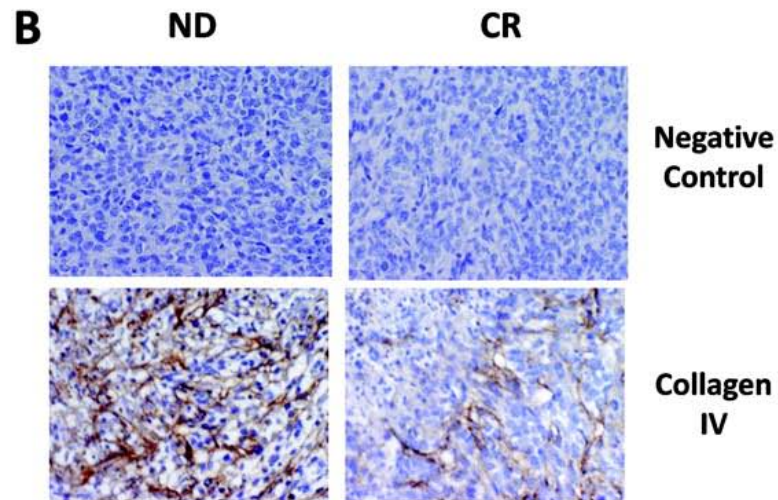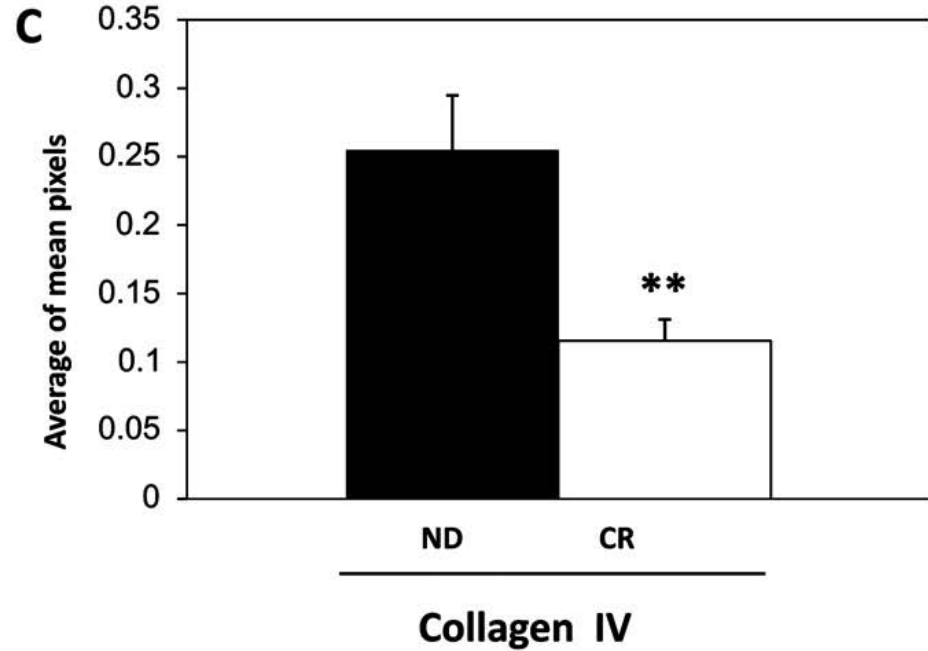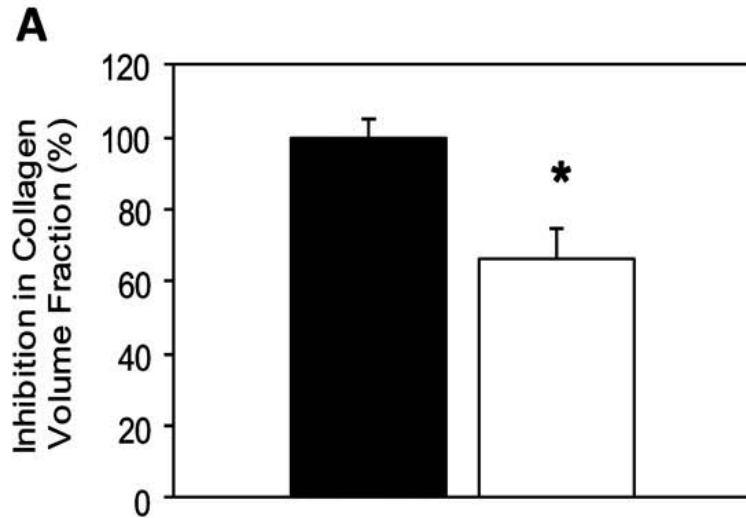

De Lorenzo M S et al. Carcinogenesis 2011;32:1381-1387

Carcinogenesis

Levels of TGF-β are reduced in CR mice.

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Carcinogenesis

CR mice possess reduced intratumor collagen IV expression.

De Lorenzo M S et al. Carcinogenesis 2011;32:1381-1387

Carcinogenesis