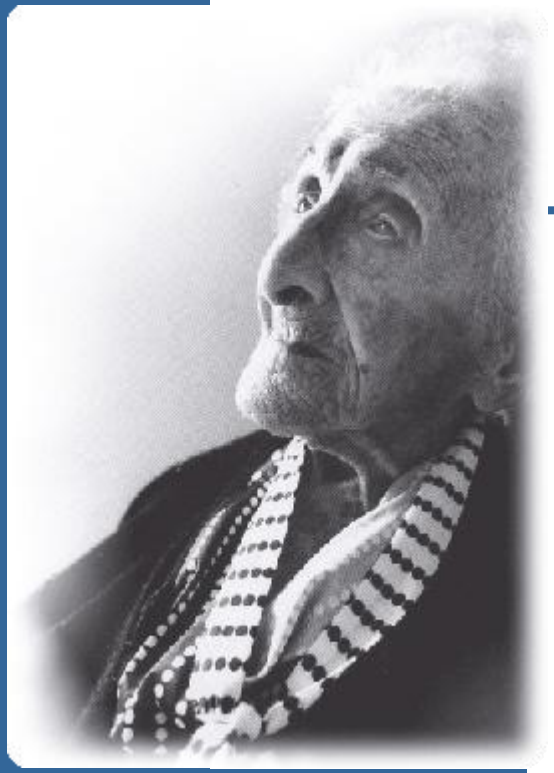

„Do not go gentle into that good night... Rage, rage against the dying of the light“

Dylan Thomas

Advances in Anti-Ageing Medicine

&

Longevity Sciences

Çimen Karasu Ph.D.

Professor in Medical Pharmacology
Head of Department of Medical Informatics
Chair: Cellular Stress Response & Signal Transduction Research Laboratory
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ESAAM and PYREMED Board Member
WAAAM Advisory Board Member

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As time goes by . . .

Greta Garbo

Ageing

- All diseases run into one - old age.

  Ralph Waldo Emerson

- To get back my youth I would do anything in the world, except take exercise, get up early, or be respectable.

  Oscar Wilde

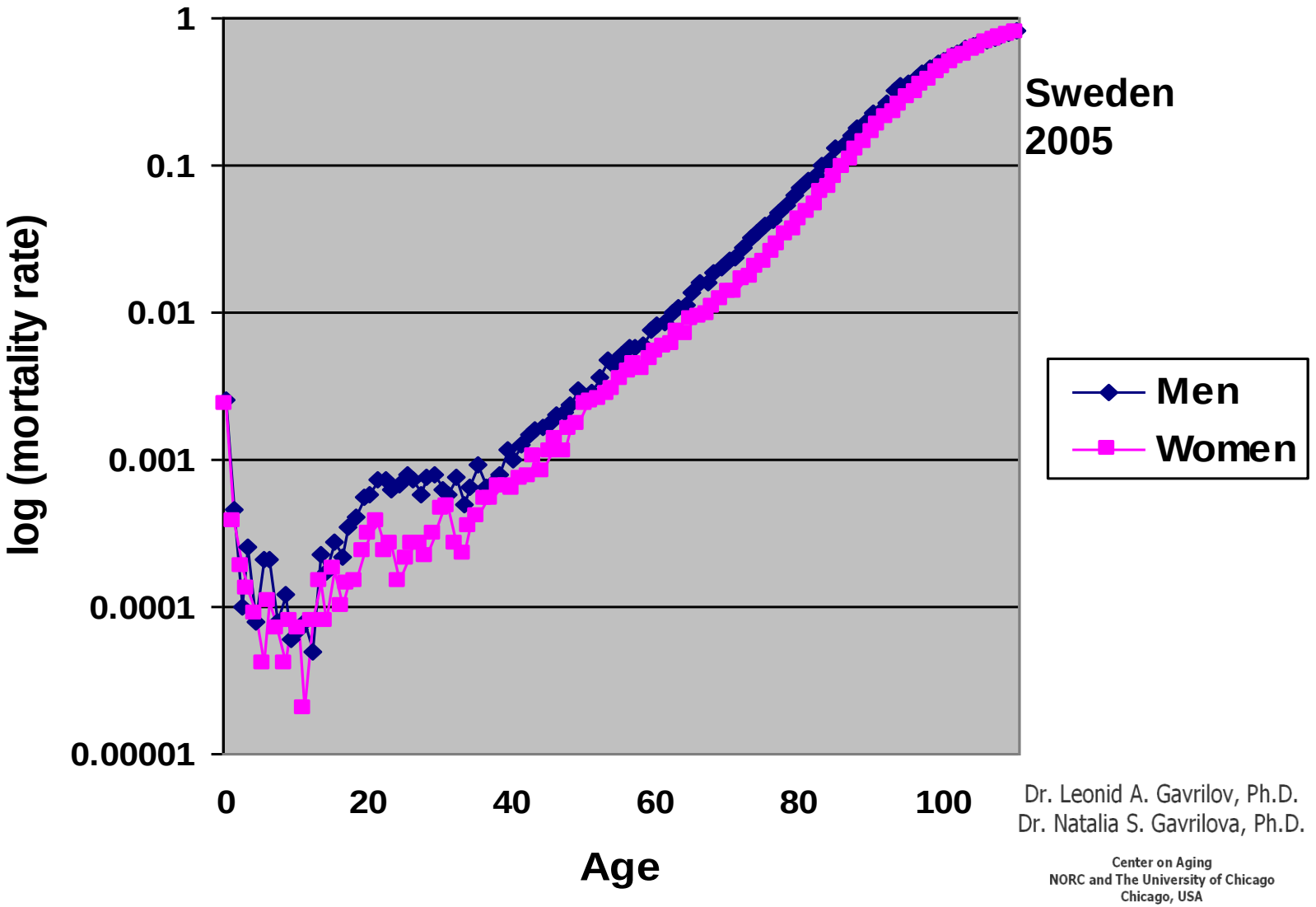
Ageing

- I don't want to achieve immortality through my work. I want to achieve it through not dying.

- I'm not afraid to die, I just don't want to be there when it happens.

Woody Allen

Mortality Rate



Dr. Leonid A. Gavrilov, Ph.D.
Dr. Natalia S. Gavrilova, Ph.D.

Center on Aging
NORC and The University of Chicago
Chicago, USA

Aging and non-aging systems

Perfect clocks having an ideal marker of their increasing age (time readings) are not aging

Progressively failing clocks are aging (although their 'biomarkers' of age at the clock face may stop at 'forever young' date)

Definition of aging in reliability theory

Ageing:

increasing risk of failure

with the passage of time (age).

Age-associated changes which lead to pathology

In Molecular, Cellular and Tissue Levels

- Loss of Molecular Fidelity
- Accumulation of Oxidation Products of Lipids and Proteins
- Thelomere Shortenings
- Decrease Capacity of Cellular Defense Mechanisms
- DNA Damage
- Increase in Mutations
- Increase in Inflammatory Reactions
- Impaired Cellular Signaling
- Decline in immunological functions
- Tissue dysfunctions

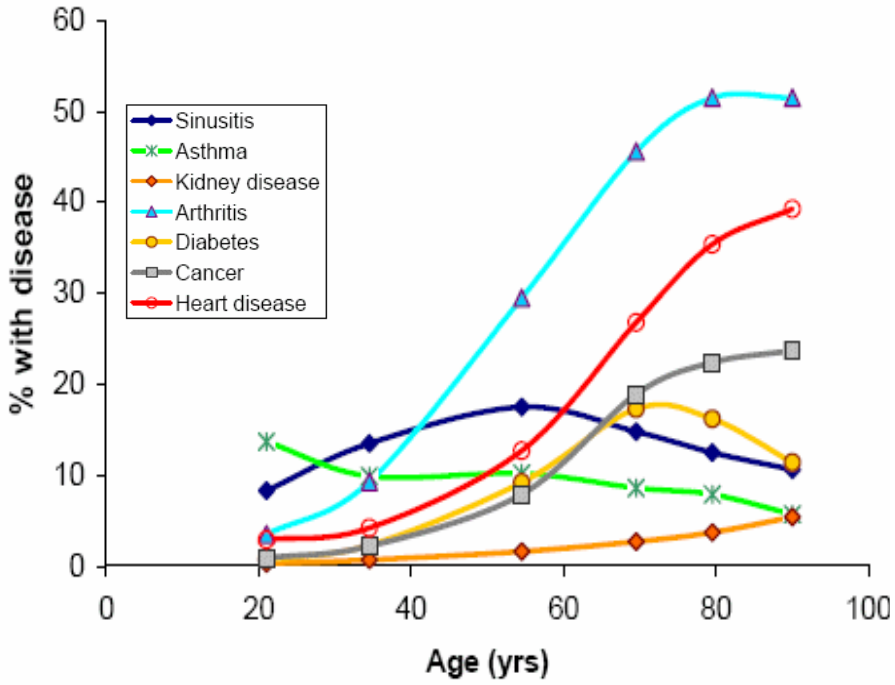
Age-associated changes which lead to pathology

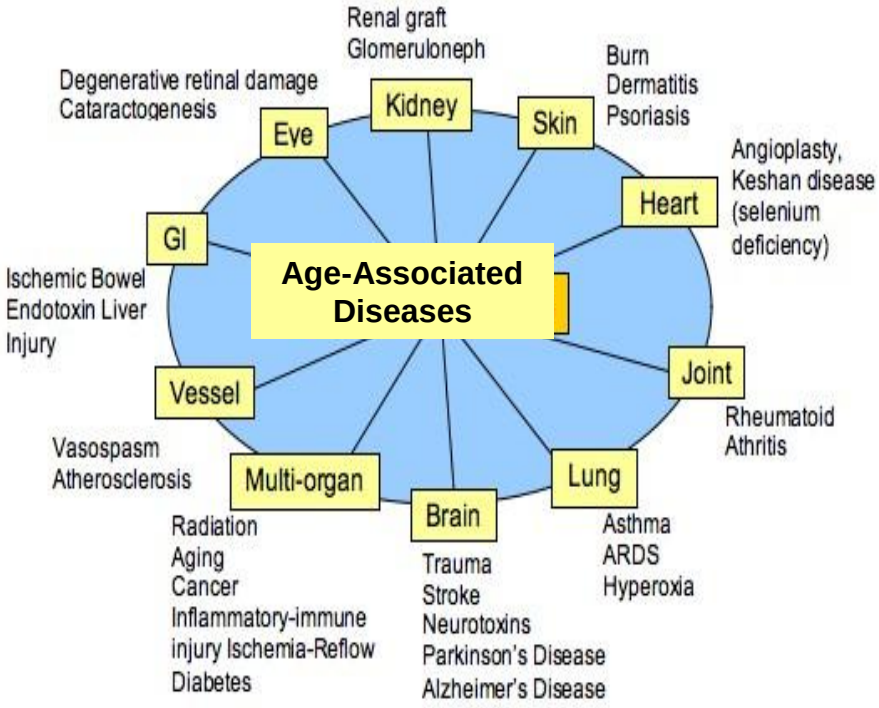
In Organ and Organism Levels

- Altered posture and reduced stature
- Greying and whitening of the hair
- Wrinkling of the skin
- Loss of accommodation
- Lens focussing of the eye
- Loss of muscular strength and physical stamina
- Imbalance
- Loss of memory
- Incontinence
- Deafness
- Reduced visual acuity
- Hardening of the arteries and increased blood pressure
- Increased probability of cerebrovascular disease
- Increased likelihood of renal failure, dementia, cancer
- Type II diabetes
- Osteoporosis, osteoarthritis
- Blindness from cataracts or retinopathy

Aging and Age-Related Disease

National Center for Health Statistics, Data Warehouse on Trends in Health and Aging





The incidence of a number of pathologies increases with age and we become more susceptible to certain diseases

Free Radical Research, December 2006; 40(12): 1230–1238

informa
healthcare

Theories of biological aging: Genes, proteins, and free radicals

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Laboratory of Cellular Ageing, Department of Molecular Biology, Danish Centre for Molecular Gerontology, University of Aarhus, Aarhus-C, Denmark

Accepted by Dr T. Grune

(Received 15 June 2006)

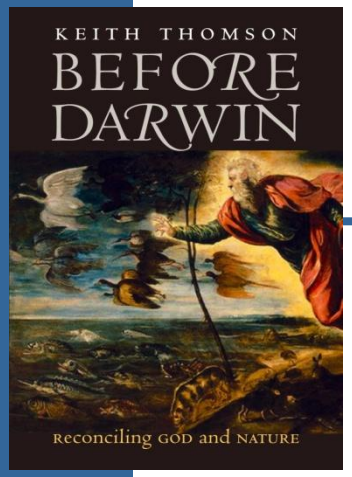
Abstract

Traditional categorization of theories of aging into programmed and stochastic ones is outdated and obsolete. Biological aging is considered to occur mainly during the period of survival beyond the natural or essential lifespan (ELS) in Darwinian terms. Organisms survive to achieve ELS by virtue of genetically determined longevity assuring maintenance and repair systems (MRS). Aging at the molecular level is characterized by the progressive accumulation of molecular damage caused by environmental and metabolically generated free radicals, by spontaneous errors in biochemical reactions, and by nutritional components. Damages in the MRS and other pathways lead to age-related failure of MRS, molecular heterogeneity, cellular dysfunctioning, reduced stress tolerance, diseases and ultimate death. A unified theory of biological aging in terms of failure of homeodynamics comprising of MRS, and involving genes, milieu and chance, is acquiring a definitive shape and wider

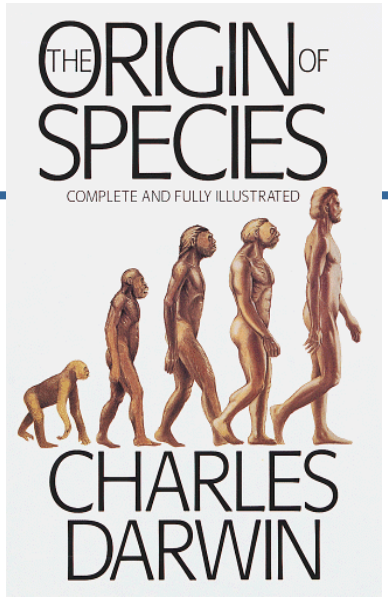
Biology Viewpoint on Aging

- For a much smaller group of scientists (naturalists, zoologists, some biologists) very familiar with life span characteristics of many non-human species, the overwhelming observational impression is that complex organisms are ***designed*** to have a limited and very species-specific life span.

EVOLUTION THEORY



Before Darwin (~1850),

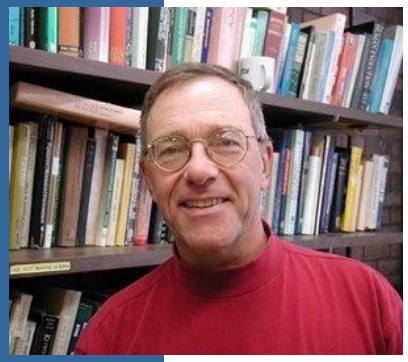


After Darwin (1859),

- Darwin's theory published in 1859 ***The Origin of Species*** has two elements:
  - ***Fact of evolution***: Did evolution occur? Are current species descended from earlier, generally simpler species? Our certainty that evolution has occurred has steadily increased. There is essentially no *scientific* disagreement.
  - ***Mechanics of evolution***: How does evolution work? What factors are important in determining which features are incorporated into an organism's design? Discrepancies between observations and Darwinian mechanics appeared immediately and additional discrepancies appeared later. Our certainty regarding Darwinian mechanics has decreased over time. Alternative adjustments or modifications to Darwinian mechanics have been proposed, some of which support aging-by-design.

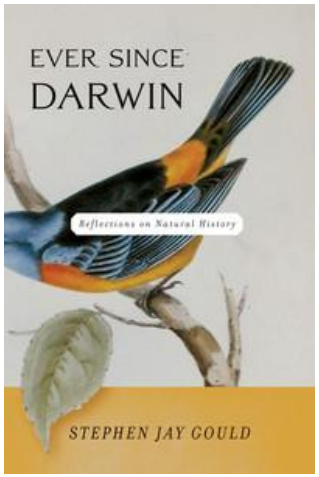
Darwin's Dilemma

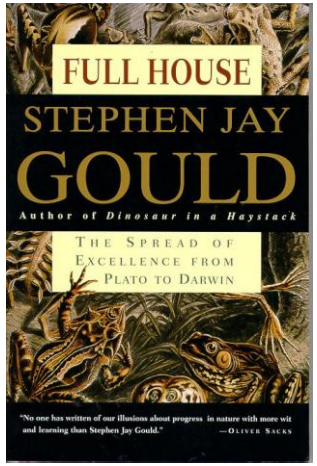
- Darwin's natural selection or "survival of the fittest" theory was obviously incompatible with feature theories of aging. No plausible way aging or other designed life span ***limitation*** assists individual ***survival*** or propagation. Cited at the time as evidence Darwin's theory was incorrect.
- A number of other apparent natural selection incompatibilities, especially in the area of behaviours, have been observed.
- This incompatibility has affected aging theories for nearly 150 years. Any feature theory of aging must invoke at least an adjustment to "Darwinian" natural selection theory.



Douglas J. Futuyma

EVOLUTION'S VOYAGE • EVOLUTION'S VOYAGE •

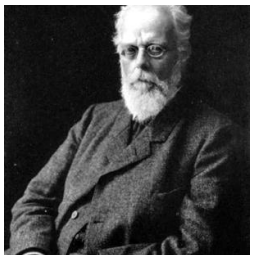




Benefits of Life Span Limitation

- A number of plausible benefits of a design-limited life span have been proposed:
  - Aids evolution process by shifting resources to younger, more evolved members of population (Weissmann 1882)

In 1882, August Weismann, an Austrian biologist, proposed a feature theory in which animals were genetically programmed to die. Purpose was to enhance the process of evolution. The "programmed death" theory achieved little scientific support primarily because of the conflict with Darwin's theory.



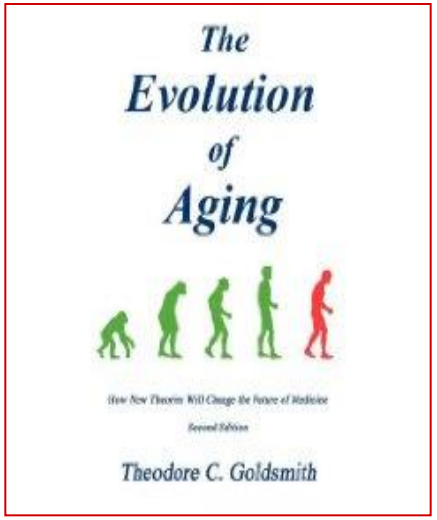
  - Reduces possibility of extinction by overpopulation (Mittledorf)
  - Aids evolution process by challenging older individuals (Schulachev)
  - Aids evolution, especially of features like intelligence and immunity (Goldsmith)
  - Prevents domination of the gene pool by a few older individuals
  - Etc., etc.
- Proposed evolution theory adjustments (all dilute individual benefit requirement):
  - Selfish gene theory (Dawkins 1975)
  - Group selection theories (~1962)
  - Evolvability theories (~1996)

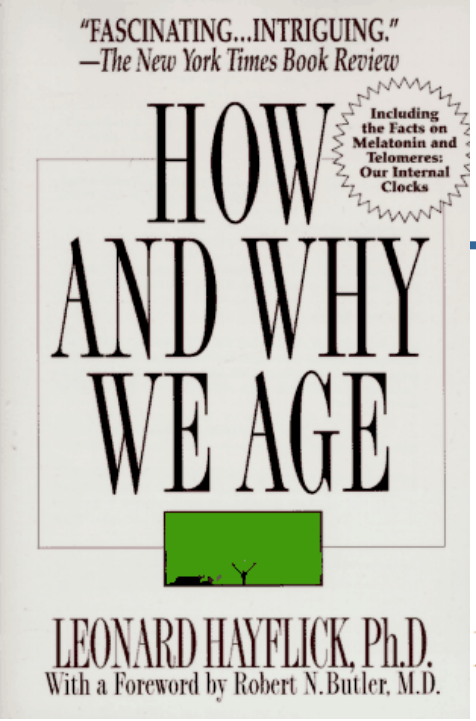
Evolvability and Aging

- Traditional Darwinism assumes all organisms have the same capacity for evolution. However, developments in genetics suggest complex (sexually reproducing) organisms have evolved improvements in their ability to evolve (adapt to their environments).
- Evolvability issues are relatively new (~1996) and may eventually result in major changes in the way we think about evolution.
- All the discrepancies have evolvability explanations.
- Aging-by-design and biological suicide have multiple evolvability benefits.

Aging – by- design

- Believers in aging-by-design tend to be much more optimistic regarding anti-aging medicine. A design can be modified. Most pharmaceuticals are intended to alter or compensate for some aspect of human design.





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Experimental Gerontology

Experimental Gerontology 38 (2003) 1231–1241

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Living forever and dying in the attempt

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Abstract

Since the first cell culture was set at the beginning of the twentieth century it was believed that all cultured cells, if provided with the proper conditions, would replicate indefinitely. Sixty years later we overthrew this dogma by finding that normal cells have a finite capacity to replicate and that only abnormal or cancer cell populations can replicate indefinitely. We interpreted these findings to bear on our understanding of the aging process. If, as had been previously thought, normal cells can replicate indefinitely, then age changes could not have an intracellular origin. Our findings demonstrated that, on the contrary, age changes do have an intracellular origin. The hundreds of changes that were subsequently found to precede the loss of replicative capacity have been interpreted to be age changes and the finitude of replication to be an expression of longevity determination. Subsequent findings by others have determined the molecular mechanism that governs the finitude of normal cell replicative capacity and how immortal cancer cells escape this inevitability. Thus, key events in our understanding of aging, longevity determination and cancer have been revealed.

Keywords: Cell culture; Longevity determination; Senescence; Aging; Immortalization; Telomeres; Telomerase

Mechanisms of Ageing and Development 129 (2008) 467–474

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journal homepage: www.elsevier.com/locate/mechagedev

Review

Cellular senescence and organismal aging

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Cellular senescence
Aging
Telomeres

ABSTRACT

Cellular senescence, first observed and defined using *in vitro* cell culture studies, is an irreversible cell cycle arrest which can be triggered by a variety of factors. Emerging evidence suggests that cellular senescence acts as an *in vivo* tumor suppression mechanism by limiting aberrant proliferation. It has also been postulated that cellular senescence can occur independently of cancer and contribute to the physiological processes of normal organismal aging. Recent data have demonstrated the *in vivo* accumulation of senescent cells with advancing age. Some characteristics of senescent cells, such as the ability to modify their extracellular environment, could play a role in aging and age-related pathology. In this review, we examine current evidence that links cellular senescence and organismal aging.

Experimental Section

Gerontology

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Senescence, Apoptosis or Autophagy?

When a Damaged Cell Must Decide Its Path – A Mini-Review

José Miguel Vicencio[a–d] Lorenzo Galluzzi[a–c] Nicolas Tajeddine[a–c]
Carla Ortiz[a, c, d] Alfredo Criollo[a–d] Ezgi Tasdemir[a–c] Eugenia Morselli[a–c]
Amena Ben Younes[a–c] Maria Chiara Maiuri[a, b, e] Sergio Lavandero[d]
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[a]INSERM, U848, [b]Institut Gustave Roussy and [c]Université Paris-Sud, Paris, France; [d]Universidad de Chile, Facultades de Ciencias Químicas Farmacéuticas y de Medicina, Centro FONDAP Estudios Moleculares de la Célula, Santiago, Chile; [e]Università degli Studi di Napoli Federico II, Facoltà di Scienze Biotecnologiche, Napoli, Italy

Published online 2 October 2007

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doi:10.1093/nar/gkm681

SURVEY AND SUMMARY

DNA damage, cellular senescence and organismal ageing: causal or correlative?

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Received July 2, 2007; Revised August 16, 2007; Accepted August 17, 2007

ABSTRACT

Cellular senescence has long been used as a cellular model for understanding mechanisms underlying the ageing process. Compelling evidence obtained in recent years demonstrate that DNA damage is a common mediator for both replicative senescence, which is triggered by telomere shortening, and premature cellular senescence induced by various stressors such as oncogenic stress and oxidative stress. Extensive observations suggest that DNA damage accumulates with age and that this may be due to an increase in production of reactive oxygen species (ROS) and a decline in DNA repair capacity with age. Mutation or disrupted

capacity of detoxification, can cause oxidative damage to macromolecules including DNA. There is an emerging consensus that a progressive and irreversible accumulation of oxidative damage contributes to impaired physiological function, increased incidence of disease and thus impacts on the ageing process (3,4).

Although ageing may involve damage to various macromolecules, for those that can be replaced by their fast turnover, damage may not accumulate and therefore may not be critical. DNA, on the other hand, is the prime information molecule of the cell and nuclear DNA in particular must last the lifetime of the cell. Therefore, DNA damage represents a critical threat to cell function. If DNA damage is severe or its accumulation exceeds its elimination by DNA repair mechanisms, cellular senescence or apoptosis will occur and this may contribute to

Denham Harman, M.D., Ph.D.

Pioneering aging research for five decades

Emeritus Professor, Internal Medicine
UNMC

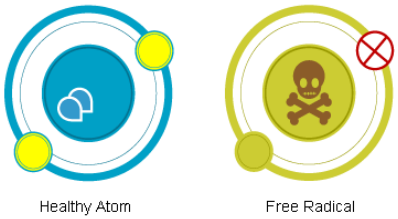
FREE RADICAL THEORY OF AGING

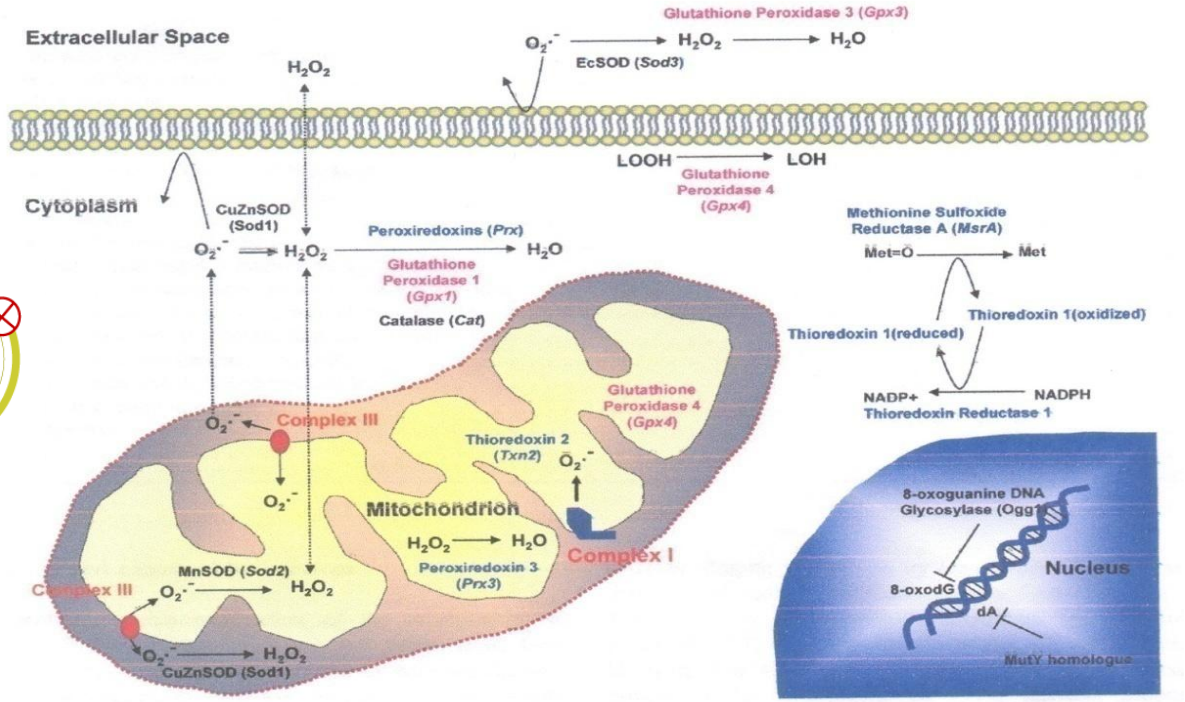
He gained international acclaim as the father of the free-radical theory of aging. He also discovered the role of antioxidants (vitamins C, E, and beta-carotene) in fighting heart disease and cancer. And today, the internist, chemist and octogenarian Dr. Denham Harman continues his pioneering work, searching for ways to extend a person's healthy life span.

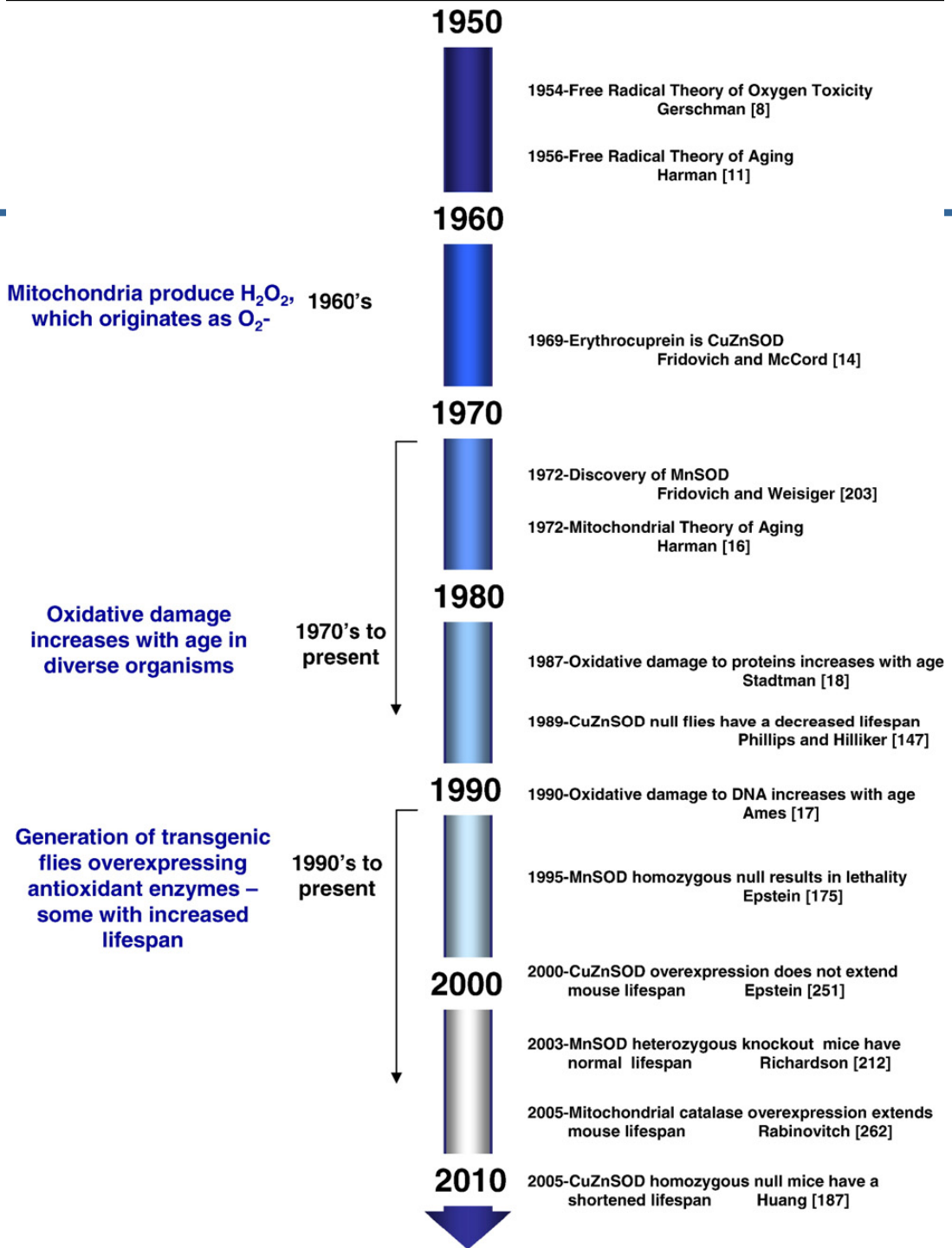
"He deserves the Nobel Prize," said Dr. Donald Ingram, acting chief of the laboratory of experimental gerontology at the National Institute on Aging in Baltimore.

The Free Radical Theory of Aging	1956, Denham Harman
Oxidative Stress Theory of Aging	1967, Denham Harman
Mitochondrial Theory of Aging	1972, Denham Harman

The free radical theory of aging argues that oxidative damage accumulates with age and drives the aging process..






1950
1954-Free Radical Theory of Oxygen Toxicity
Gerschman [8]
1956-Free Radical Theory of Aging
Harman [11]
1960
Mitochondria produce H_2O_2, which originates as O_2-
1960's
1969-Erythrocuprein is CuZnSOD
Fridovich and McCord [14]
1970
1972-Discovery of MnSOD
Fridovich and Weisiger [203]
1972-Mitochondrial Theory of Aging
Harman [16]
1980
Oxidative damage increases with age in diverse organisms
1970's to present
1987-Oxidative damage to proteins increases with age
Stadtman [18]
1989-CuZnSOD null flies have a decreased lifespan
Phillips and Hilliker [147]
1990
1990-Oxidative damage to DNA increases with age
Ames [17]
Generation of transgenic flies overexpressing antioxidant enzymes – some with increased lifespan
1990's to present
1995-MnSOD homozygous null results in lethality
Epstein [175]
2000
2000-CuZnSOD overexpression does not extend mouse lifespan Epstein [251]
2003-MnSOD heterozygous knockout mice have normal lifespan Richardson [212]
2005-Mitochondrial catalase overexpression extends mouse lifespan Rabinovitch [262]
2010
2005-CuZnSOD homozygous null mice have a shortened lifespan Huang [187]

Free radical theory of Aging goes hand-in-hand with other theories of Aging

EVOLUTIONARY THEORIES

Disposable Soma

Antagonistic Pleiotropy

Mutation Accumulation

Accumulation of Free Radical DAMAGES

MOLECULAR THEORIES

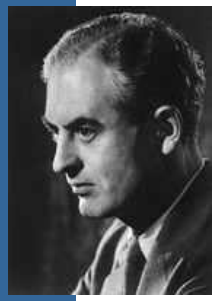
Codon Restriction

Error Catastrophe

Somatic Mutation

Differentiation

Gene Regulation



Aging has been defined as the collection of changes that render human progressively more likely to die (Medawar, 1952).

CELLULAR THEORIES

Free Radical-Oxidative Metabolism

Mitochondial Theory of Aging

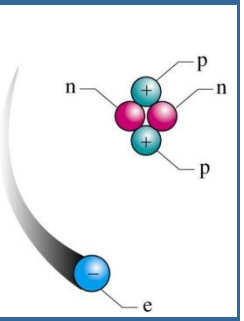
Wear and Tear

- Glycoxidation Theory of Aging
- Lipoxidation Theory of Aging
- Inflammation Theory of Aging

Apoptosis

Senescence

What are the Prooxidants ?



Free Radicals:

Any species that contain one or more unpaired electrons, very unstable, try to become stable, either by accepting or donating an electron,

$R_3C\cdot$	Carbon-centered
$R_3N\cdot$	Nitrogen-centered
$R\text{-}O\cdot$	Oxygen-centered
$R\text{-}S\cdot$	Sulfur-centered

Non-Radicals:

- ✓ Species that have strong oxidizing potential,
- ✓ Species that favor the formation of strong oxidants

H_2O_2	Hydrogen peroxide
$HOCl^-$	Hypochlorous acid
O_3	Ozone
$^1O_2$	Singlet oxygen
$ONOO^-$	Peroxynitrite
Me^{n+}	Transition metals

Halliwell & Gutteridge Free Radicals in Biology & Medicine, 2007

Oxygen is essential for aerobic organisms

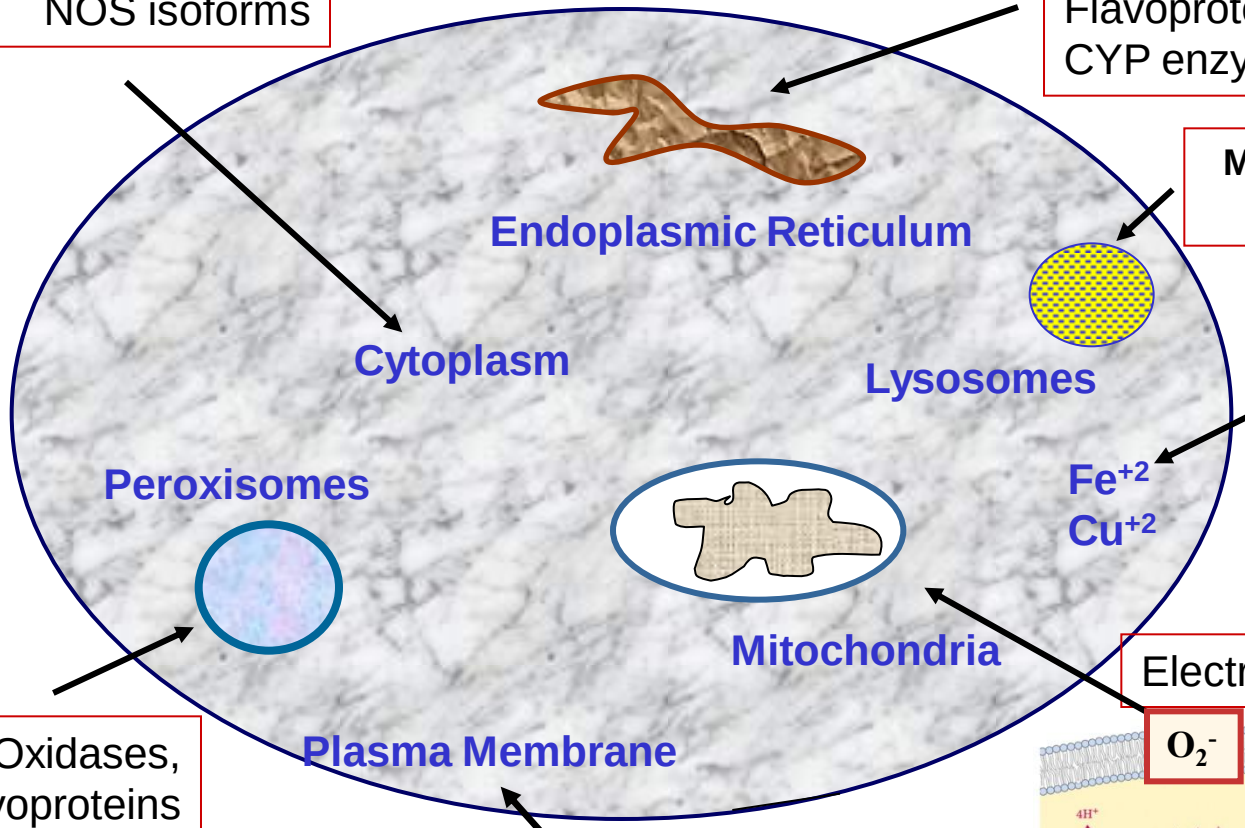
The Reactive Oxygen Species (ROS) are physiologically generated during oxidative metabolism of any aerobic organism

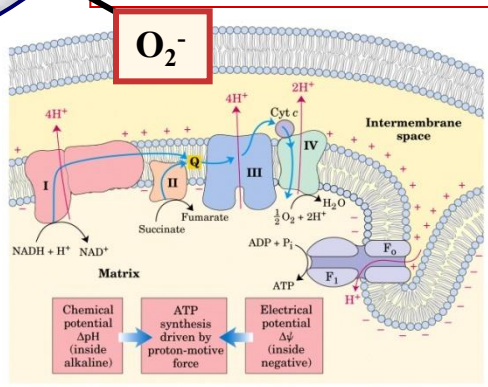
ROS

Radicals:	
$O_2 \cdot^-$	Superoxide
$OH\cdot$	Hydroxyl
$RO_2\cdot$	Peroxyl
$RO\cdot$	Alkoxyl
$HO_2\cdot$	Hydroperoxyl

Non-Radicals:	
H_2O_2	Hydrogen peroxide
$HOCl^-$	Hypochlorous acid
O3	Ozone
$^1O^2$	Singlet oxygen
$ONOO^-$	Peroxynitrite

Endogenous Source of ROS

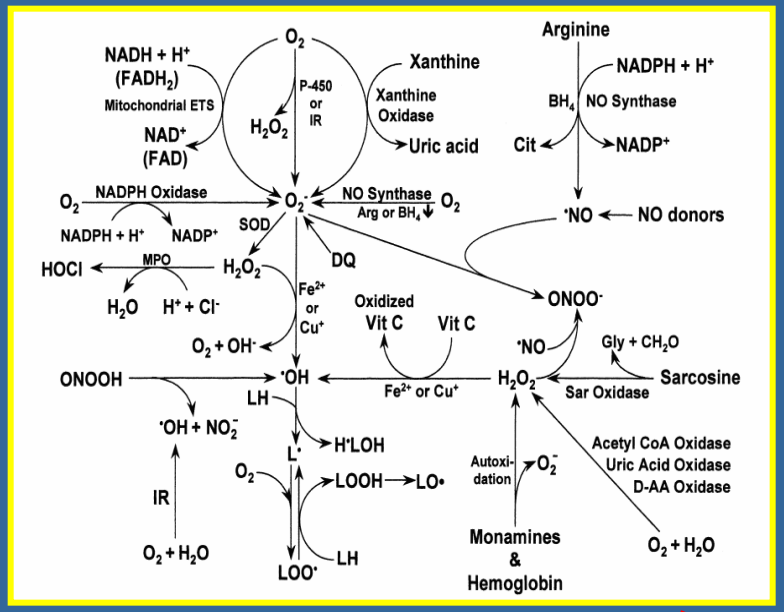




Droge W (2002) Physiol Rev 82: 47-95

ROS are generated in living cells

Mitochondrial respiratory chain
NADPH oxidase
Xanthine oxidase
Fenton reaction
Inflamatory cascades



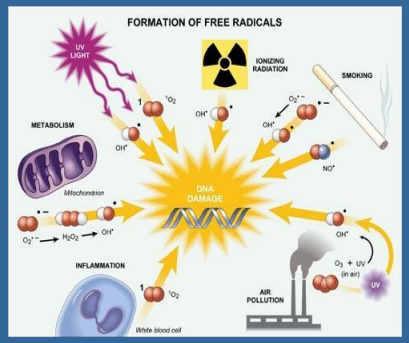
PHYSIOLOGY

Oxidation
Peroxidation
Hydroxylation
Nitration
Nitrosation

Increase of oxidative challange

Reduction of antioxidative defense

Increased Production



ROS damage the cellular constituents

PATHOLOGY

ROS generation is an essential element for certain biological responses

Droge W (2002) Physiol Rev 82: 47-95

$O_2.-$ Superoxide

control of ventilation
vasoconstriction
phagositosis

Karasu C.Free Radic Biol Med. 1999.

H_2O_2 Hydrogen peroxide

vasoconstriction
cGMP-vasorelaxation
activate several key components of the insulin signaling cascade

Brown & Griendling, FRBM, 2009.

Temple M et al; Trends in Cell Biology 2005

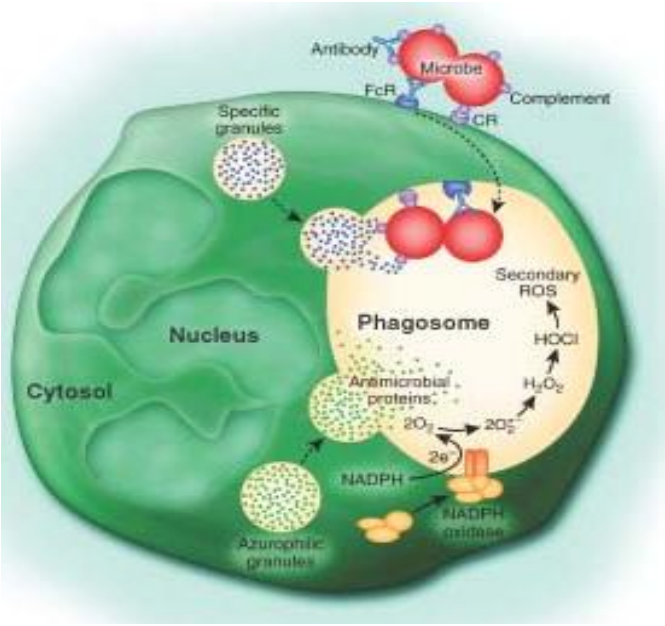
Gryglewski & Moncada, 1987.

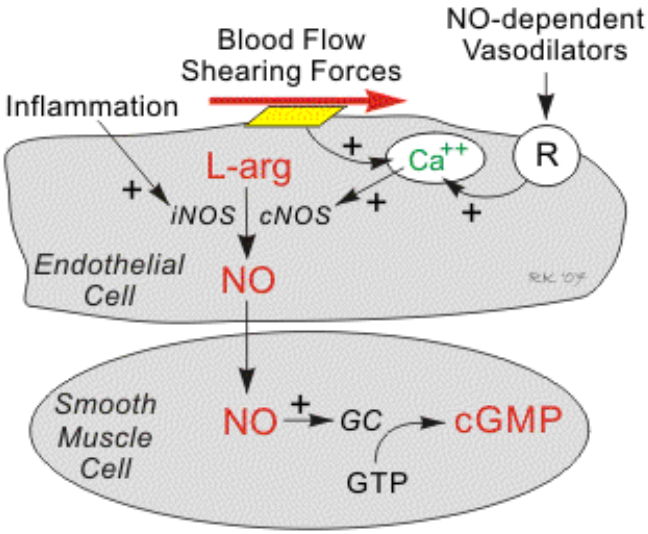
NO· Nitric oxide

cGMP- vasorelaxation
platelet inhibition

Droge W Physiol Rev 2002

REDOX HOMEOSTAZIS





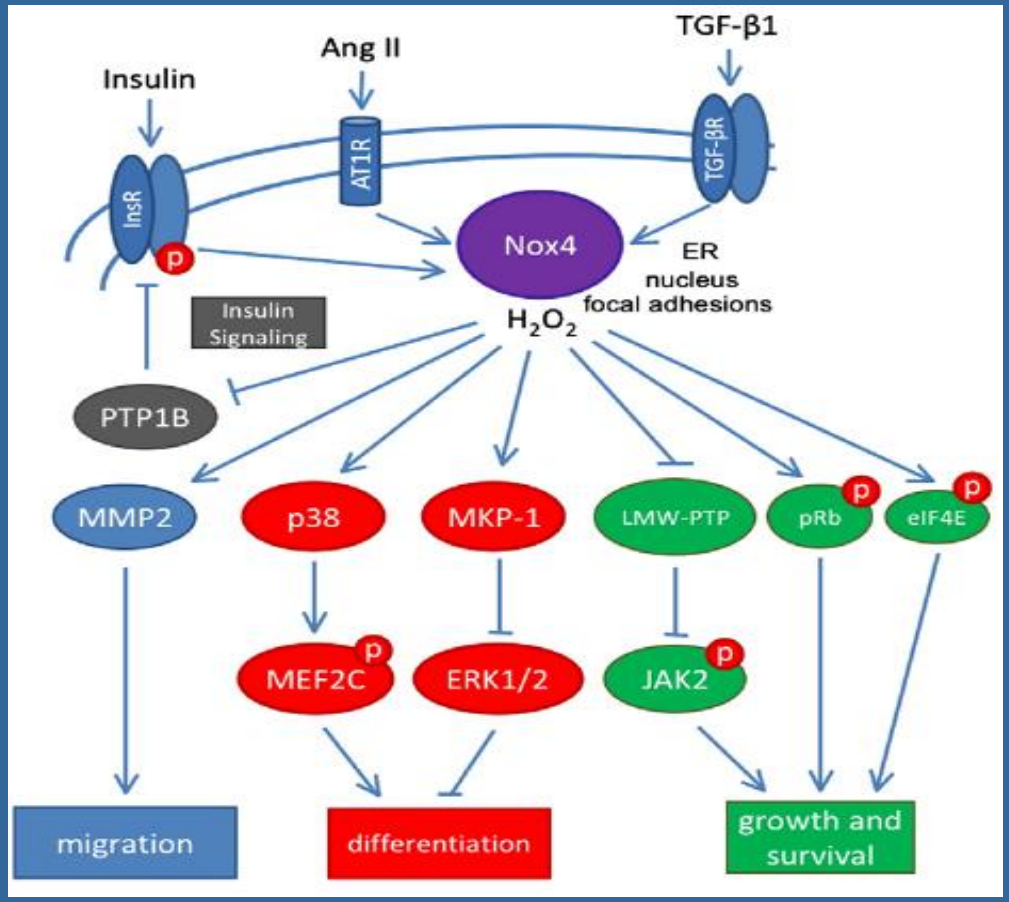
Complex signal role of ROS in the cells

Reactive Oxygen as a Second Messenger

H2O2 generation via the Nox-4 subunit of NAD(P)H oxidase….

Endogenously prduced H2O2 mimics many physiological responses of insulin

Exogenously added H2O2 has also been shown to activate several key components of the insulin signaling cascade.

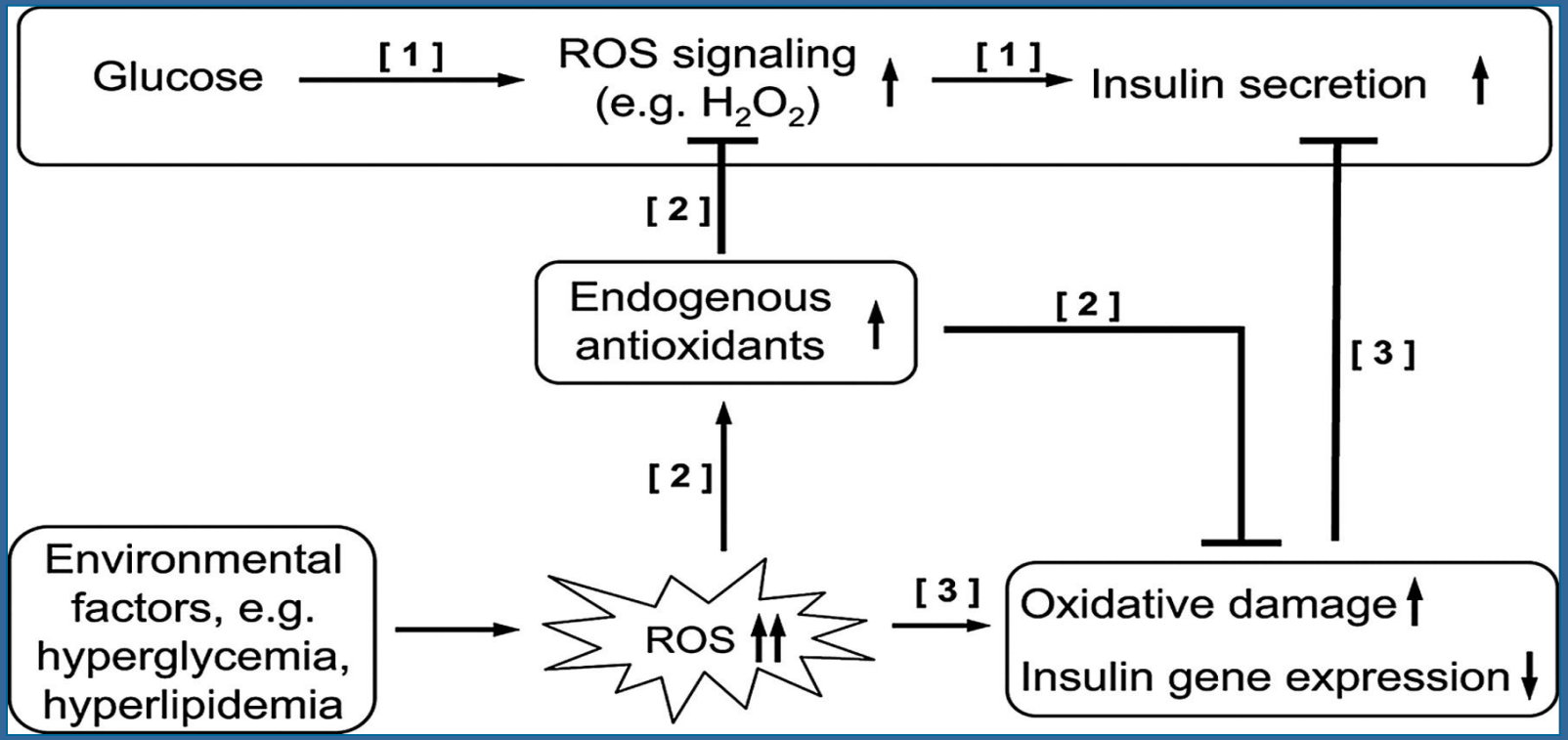


Brown & Griendling, FRBM 47: 1239 [2009]

Breakdown of physiological Signalling as a Results of Oxidative or Reductive Stress

World J Gastroentero l. 15:4137-42, 2009.

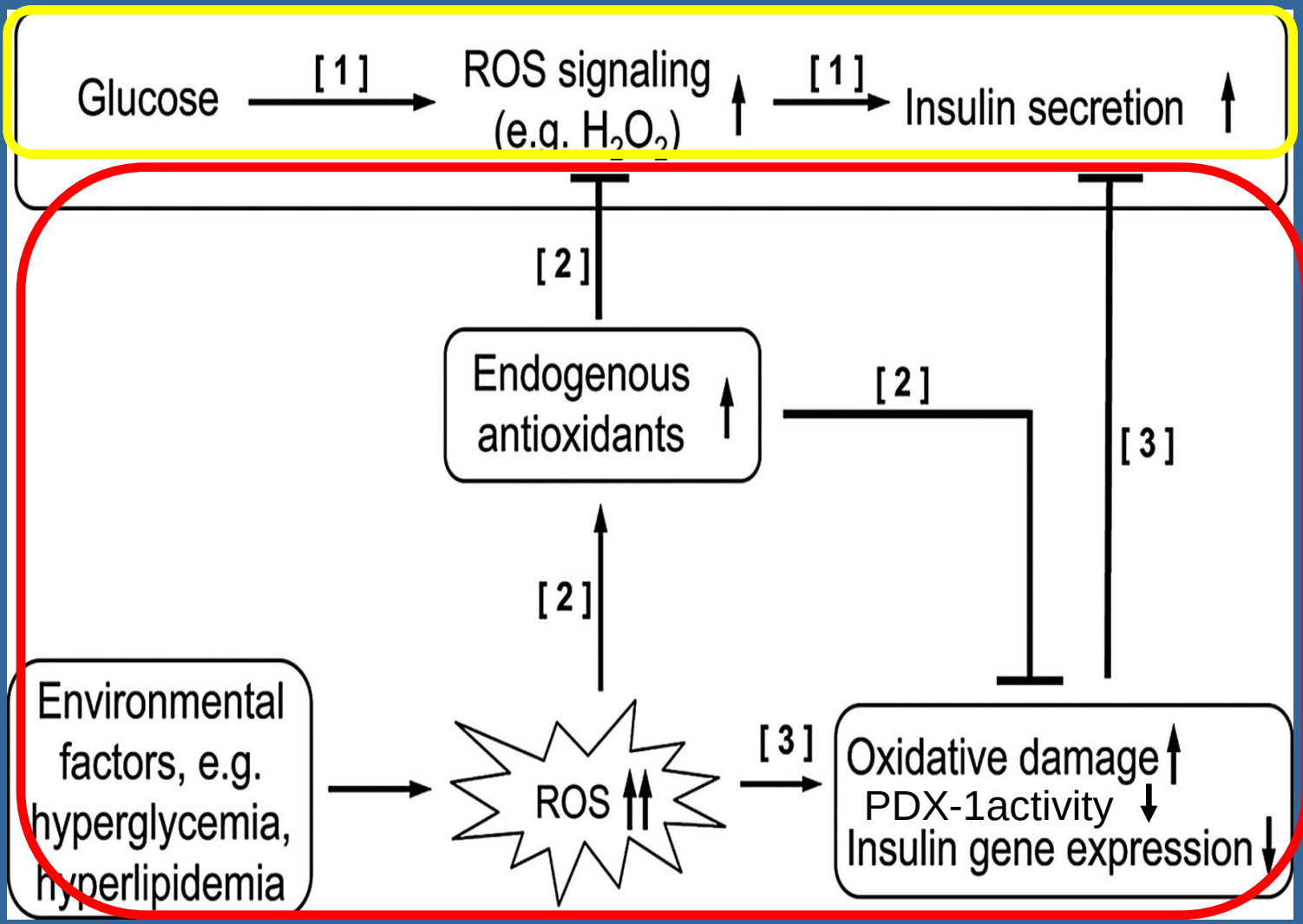
Cai H; Circulation Research 96:818-822, 2005



AGING

PANCREAS BETA-CELL

PHYSIOLOGY

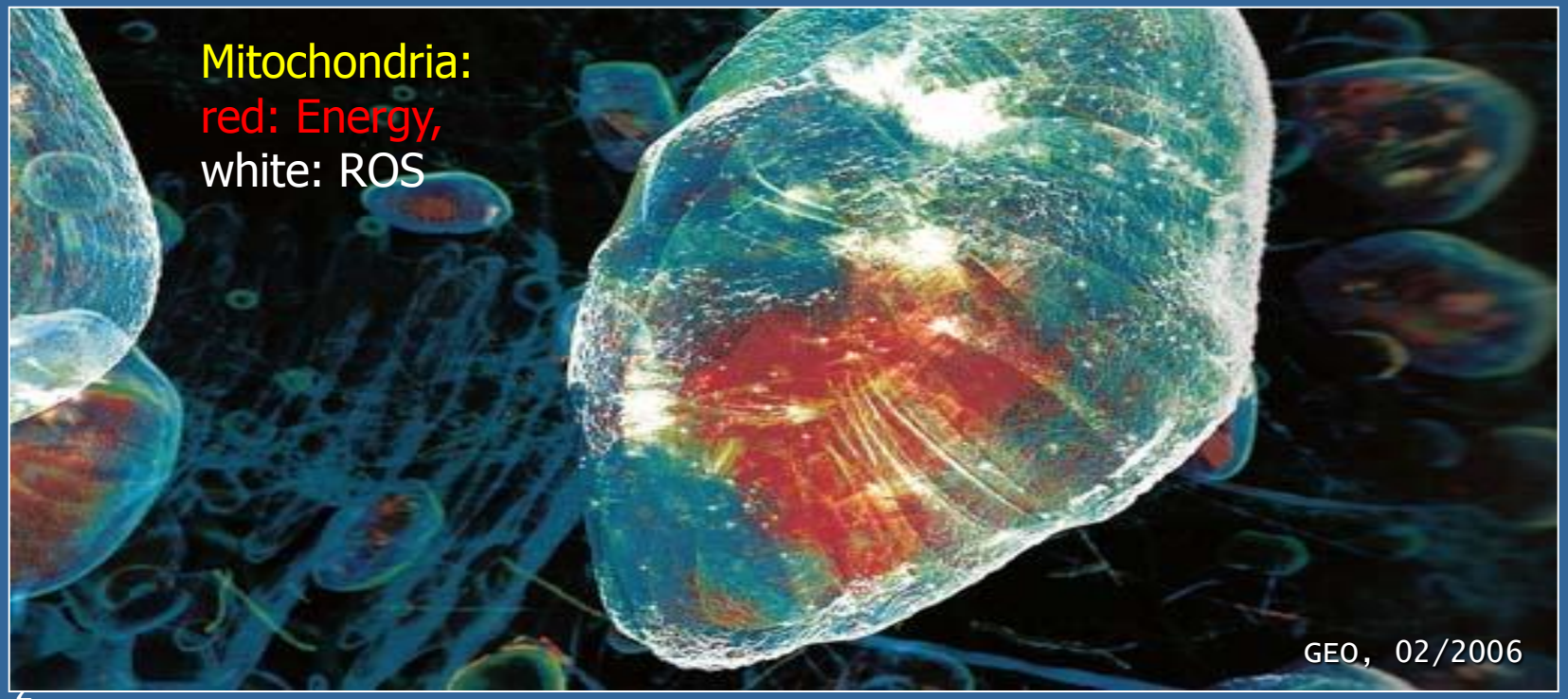


PATHOLOGY

World J Gastroenterol. 15):4137-4142, 2009.

Oxidative Stress

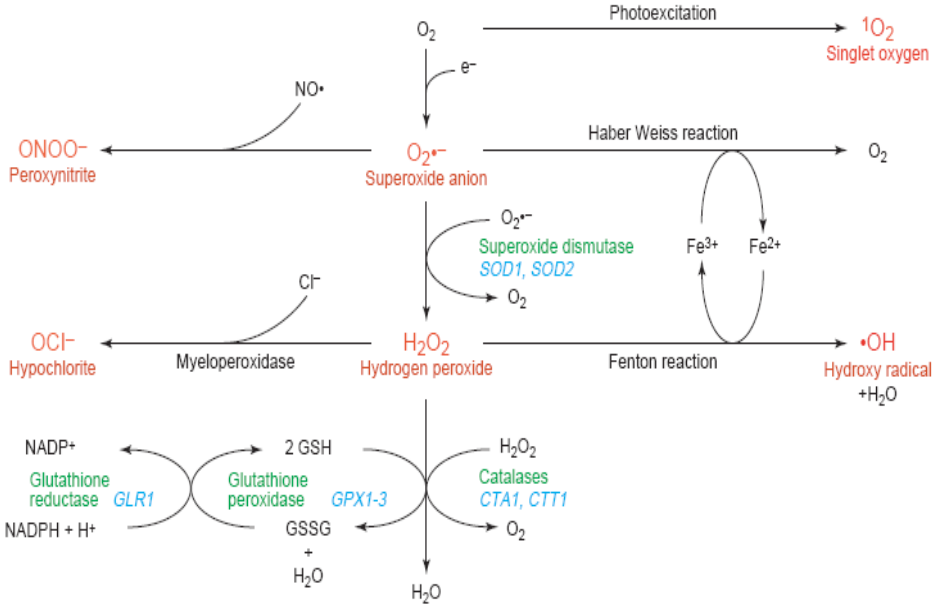
Disbalance between prooxidative and antioxidative systems with a prevaling of the former.



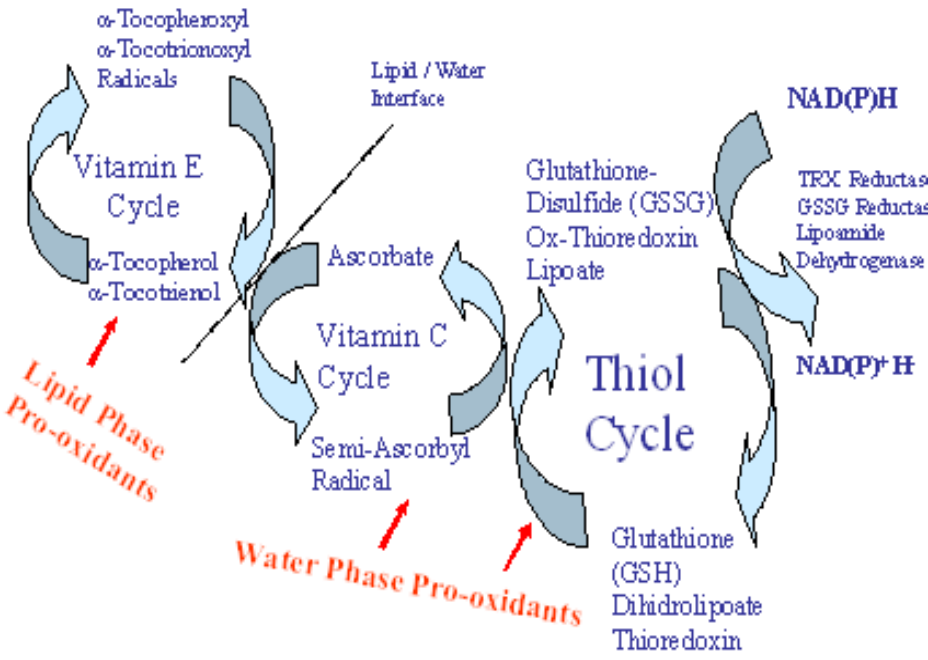
Oxidative Stress

While oxygen is ubiquitous and necessary for oxidative metabolism, the **Oxidative Stress** can occur as a result of either ROS over-production or decreased antioxidant defense

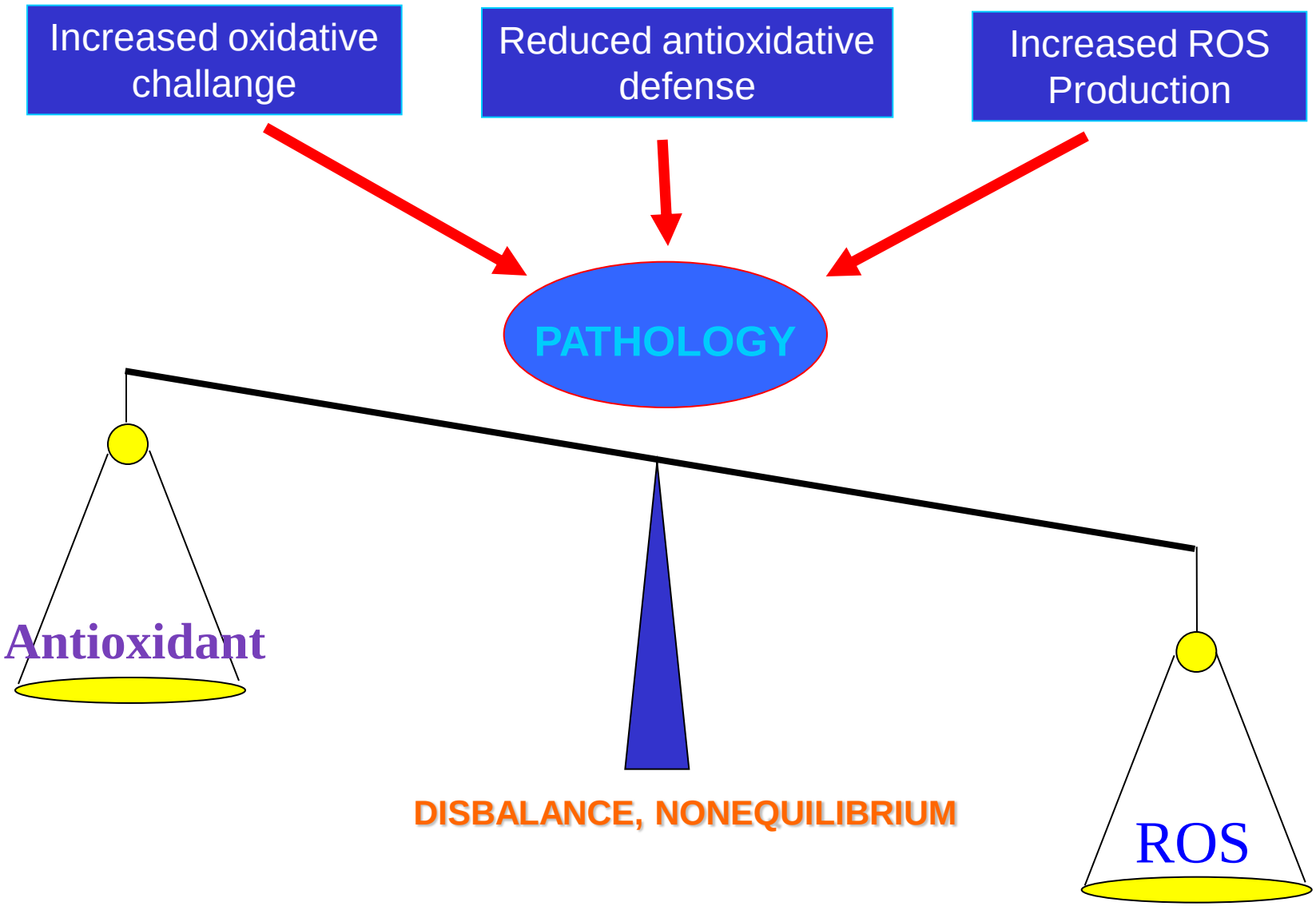
Enzymatic mechanisms

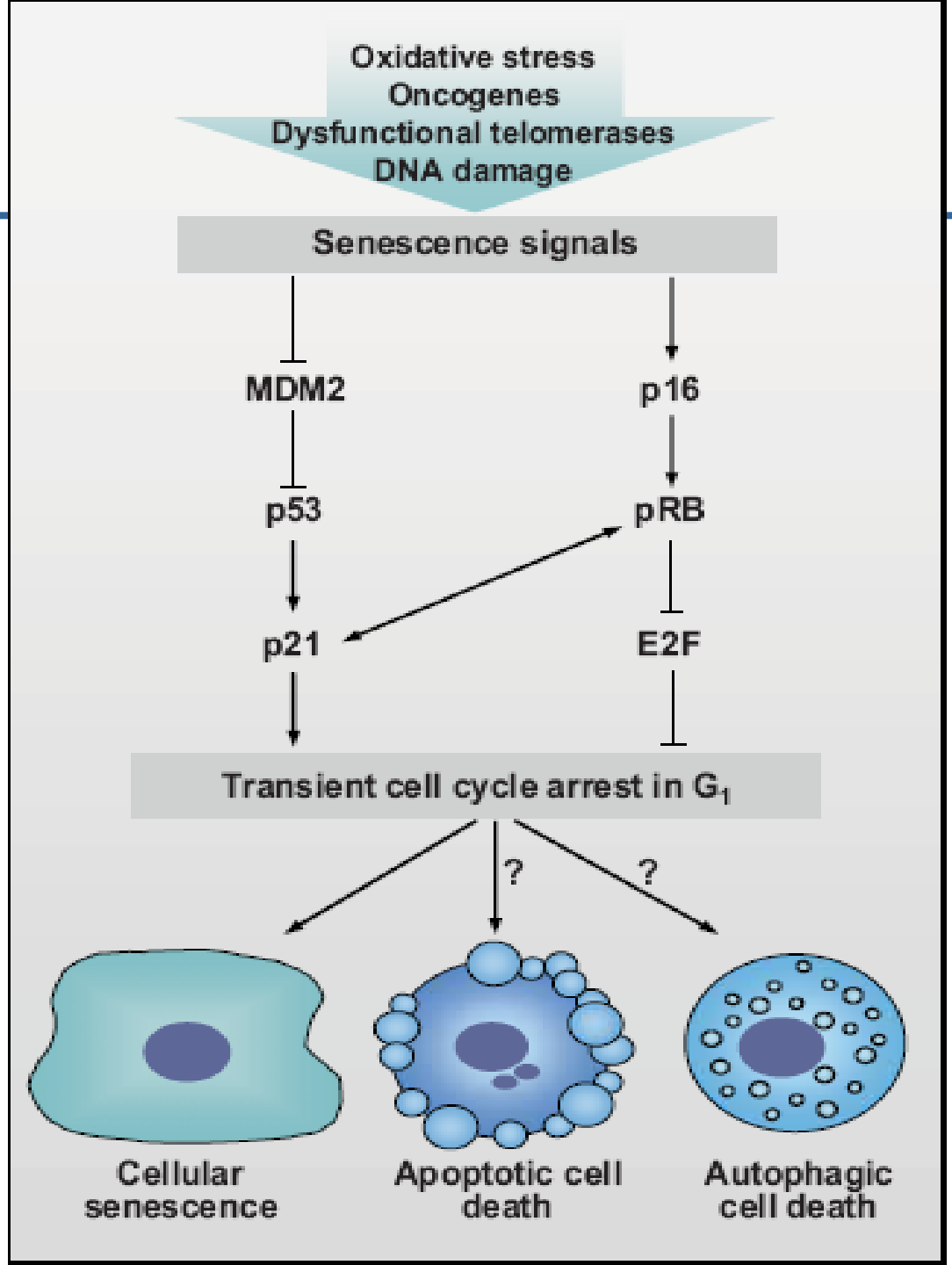


Non-enzymatic mechanisms



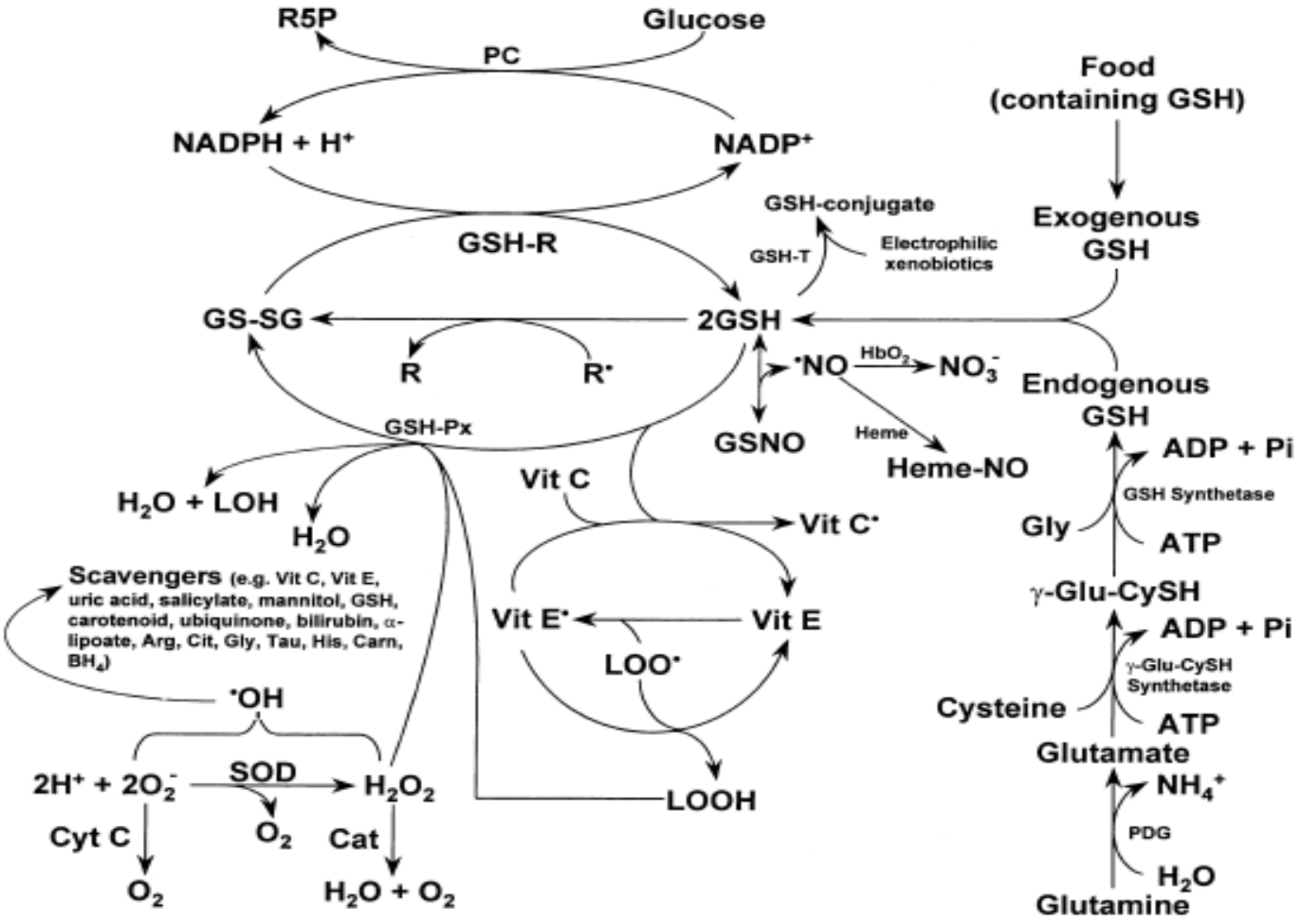
Free Radicals-induced Oxidative Stress




Oxidative stress
Oncogenes
Dysfunctional telomerases
DNA damage
Senescence signals
MDM2
p16
p53
pRB
p21
E2F
Transient cell cycle arrest in G1
?
?
Cellular senescence
Apoptotic cell death
Autophagic cell death

Antioxidants act as biological response modifiers!

Removal of oxygen and nitrogen free radicals and other ROS in mammalian cells by ANTIOXIDANT VITAMINS



Antioxidants act as biological response modifiers! to maintenance of celular redox homeostasis

Radical Formation

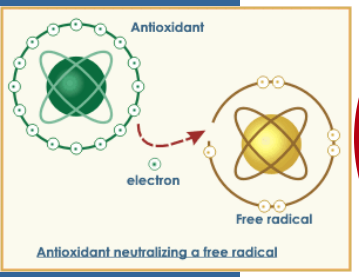
Oxidant Uptake

Oxidants

Antioxidative Defense

Antioxidants
Antiox. Enzymes

Repair
Reconstitution



Cell Death

Oxidative Damage

Adaptation

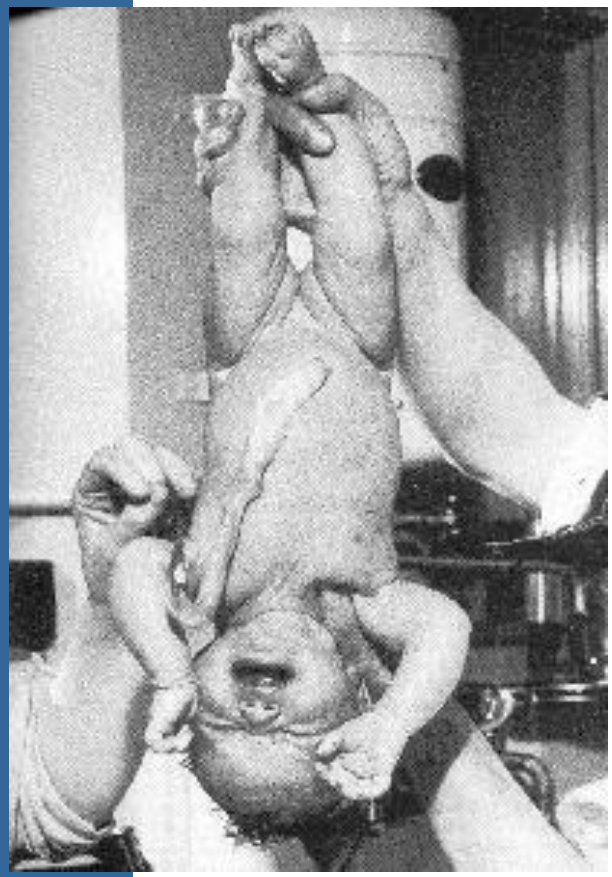
Metabolic modulation

Adaptation

Reductive Stress

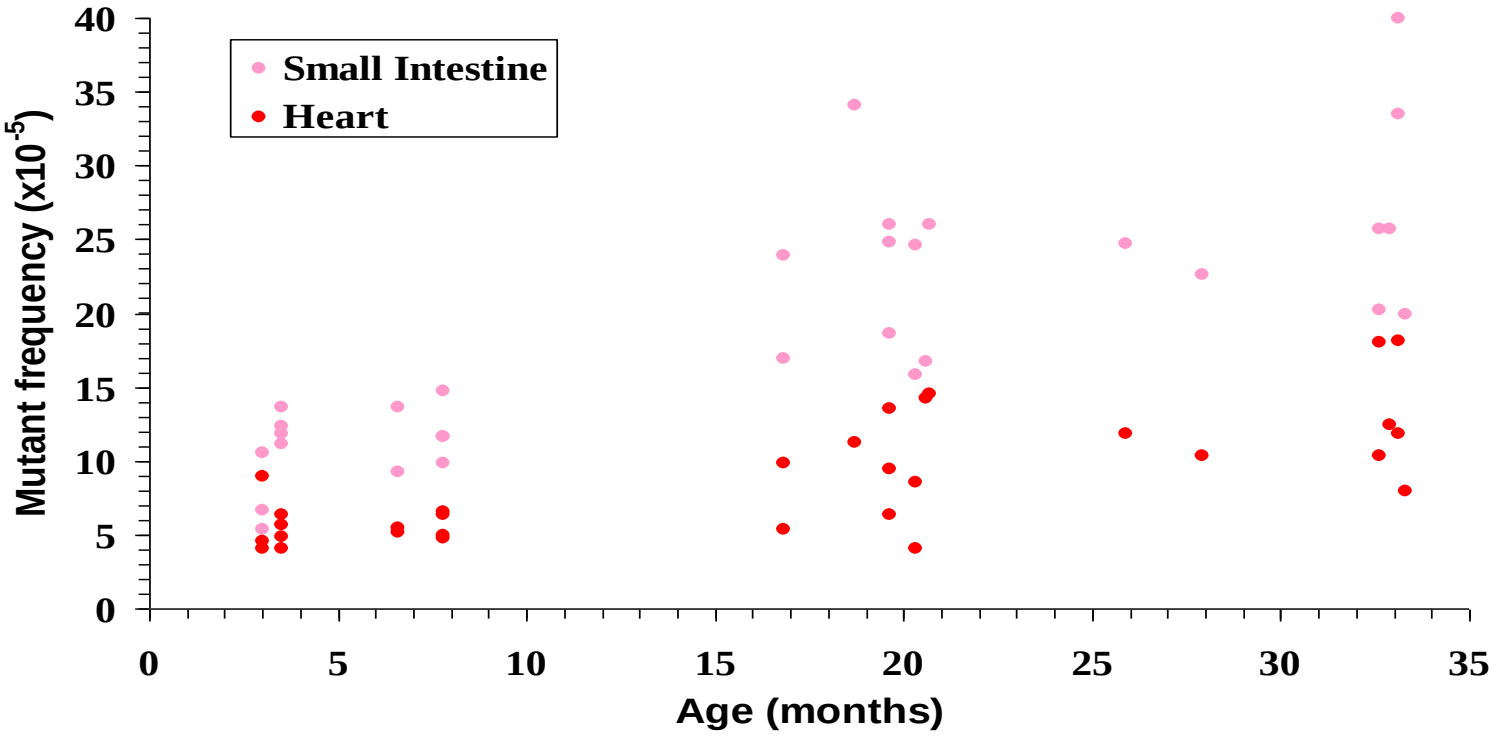
Cell Death !

Birth Process is a Potential Source of High Initial Damage



- Severe hypoxia and asphyxia just before the birth.
- oxidative stress just after the birth because of acute reoxygenation while starting to breathe.
- The same mechanisms that produce ischemia-reperfusion injury and the related phenomenon, asphyxia-reventilation injury known in cardiology.

Spontaneous mutant frequencies with age in heart and small intestine



Source: Presentation of Jan Vijg at the IABG Congress, Cambridge, 2003

Anti-Aging

TERM IS COMPLEX,

ILL-DEFINED, CONFUSING,

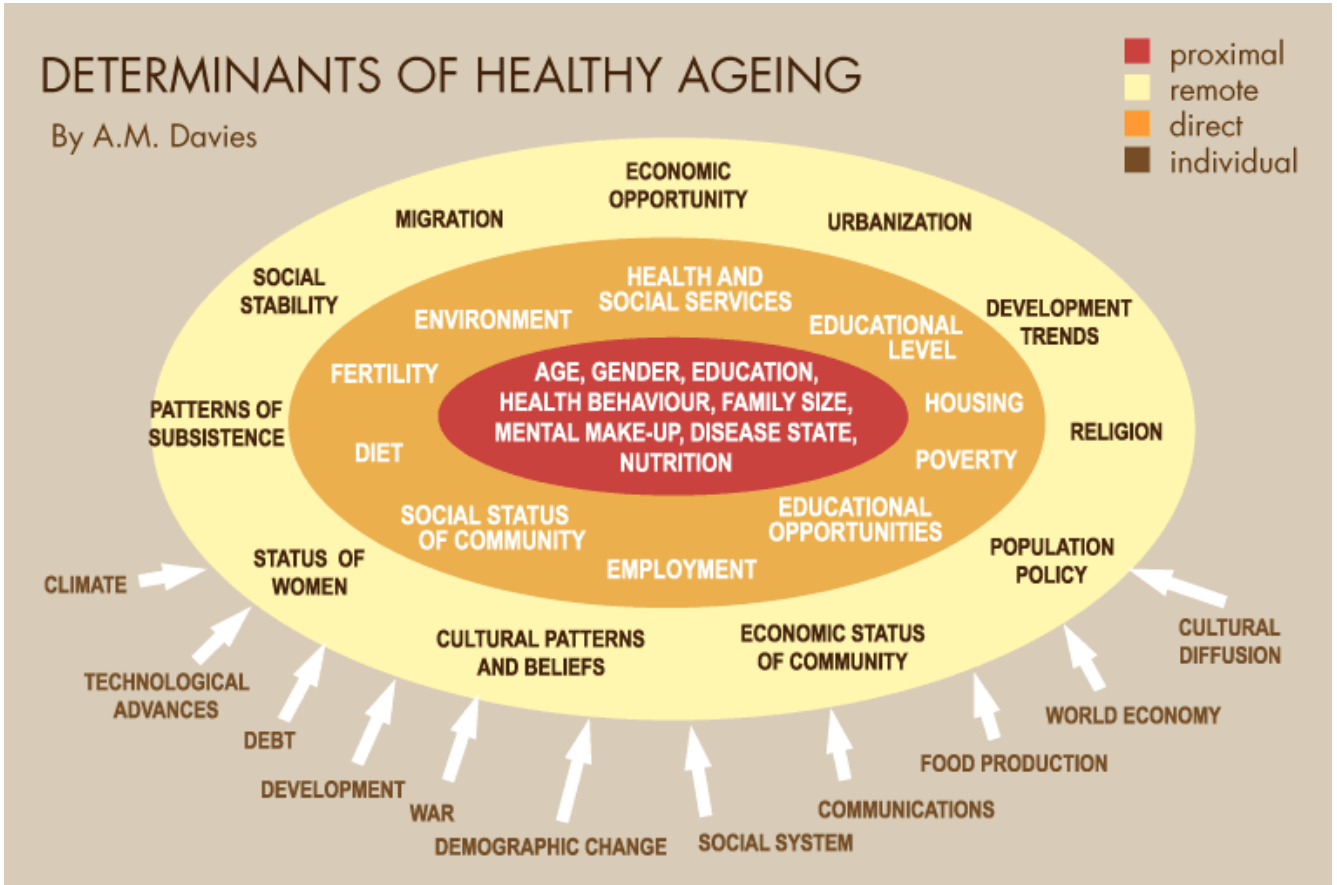
&

MISUNDERSTOOD

Anti-Ageing is “Healthy Aging” ???

'Healthy aging' is an oxymoron like a healthy dying or a healthy disease..

More accurate terms instead of 'healthy aging' would be a delayed aging, postponed aging, slow aging, or negligible aging



Contra…

✓ The anti-aging medicine movement proposes to alter the human body in order to achieve extreme longevity. To do this it has to reverse or by-pass the multiple causes of human aging.

✓ Although this anti-aging movement is relatively new, it already makes very strong claims that it will succeed.

Robin Holliday
Australian Academy of Science, Canberra, Australia
The extreme arrogance of anti-aging medicine

Holiday R, Rattan SIS. Biogerontology 11:507-11, 2010

Pro…

The past decade has witnessed remarkable advances in the field of biology. Disciplines such as **genomics** and **proteomics** have emerged to exploit our growing knowledge of the human genome and have drastically accelerated our ability to understand how the human body responds to its environment.

Susan H. Weinkle[1]**, Jay P. Tiesman**[2]
[1]University of South Florida College of Medicine,
[2]The Procter & Gamble Company, Miami, FL, USA

Genomics of Skin Aging: Practical Applications

Weinkle SH, Tiesman JP. J Drugs Dermatology 8:3, 2009

Pro…

Global gene expression profiling provides a useful means to identify key aspects of the tissue aging process, and provides information to help develop new tissue technologies...

Rosemarie Osborne, Lisa A. Mullins
The Procter & Gamble Company, Miami, FL, USA
Understanding Metabolic Pathways of Skin Anti-Aging

Osborne R, Mullins LA. J Drugs Dermatology 8:4-7, 2009

Pro…

Bioinformatics tools enable an integrated analysis of gene expression themes and pathways, which may provide new insights into the mechanisms of tissue aging and possible interventions.

Michael K. Robinson[1], Robert L. Binder[1], Christopher E.M. Griffiths[2]
[1]The Procter & Gamble Company, Miami, FL, USA
[2]Manchester Academic Health Center, Manchester, UK
Genomic-Driven Insights into Changes in Aging Skin

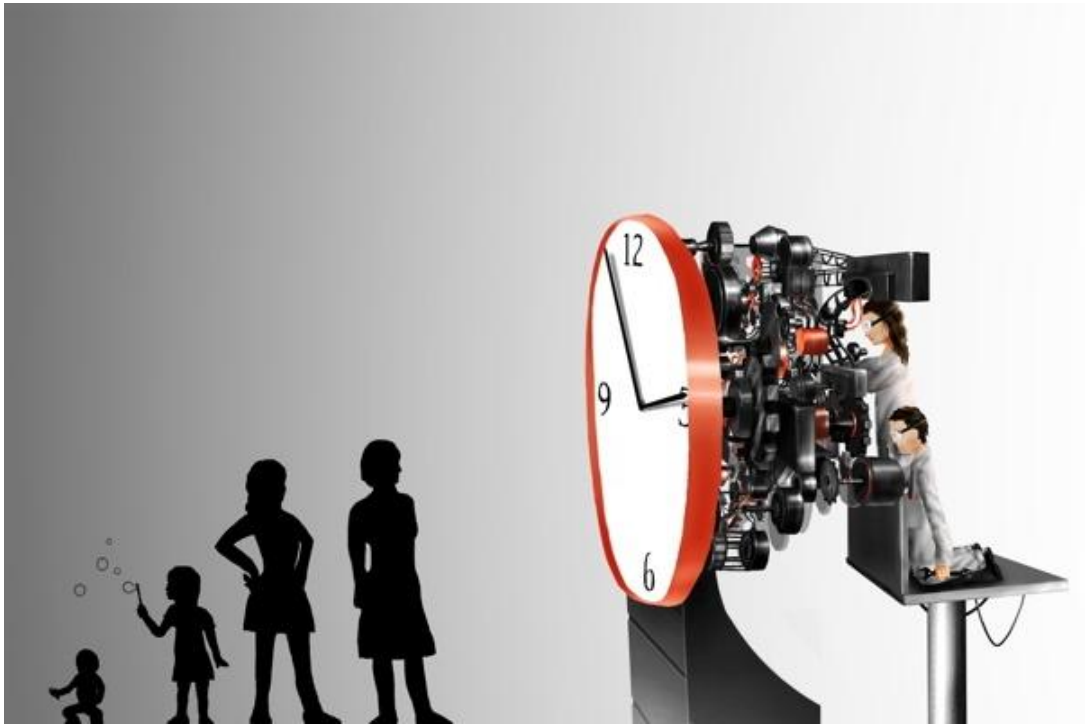
Robinson MK, Binder RL, Griffiths CEM. J Drugs Dermatology 8:8-11, 2009

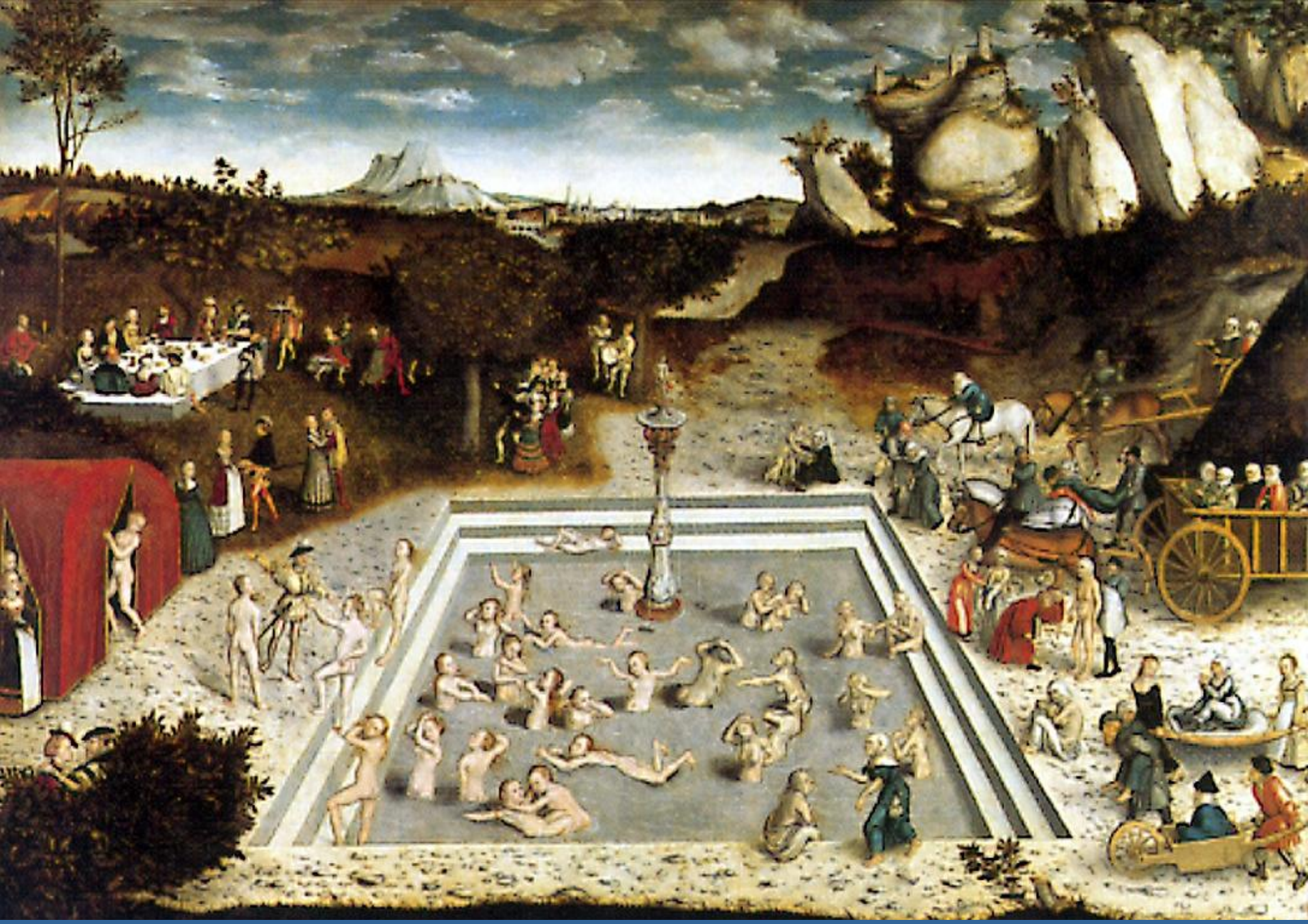
Consequence of a Succesful Biomedical War on Aging

The purpose of our studies:

to understand the mechanisms of **aging** and **longevity** in order

✓ to extend healthy and productive human lifespan.





Lucas Cranach d. Ä. The fortune of youth. 1546, National Gallery Berlin

Modern anti-aging medicine

- Prevention
- Regeneration
- Anti-aging procedures

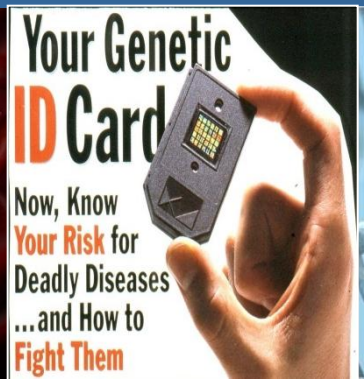
PREVENTION

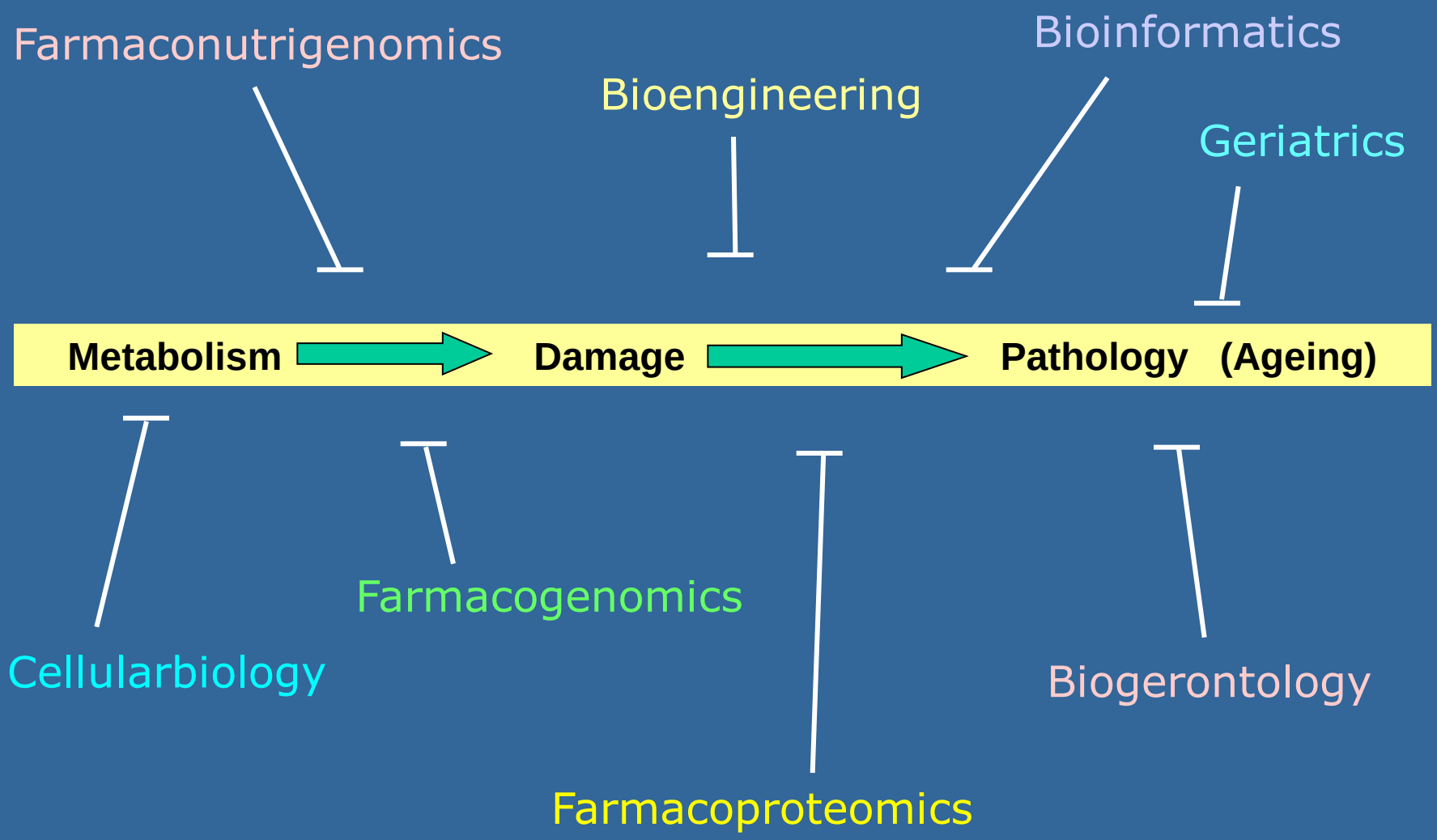
PREVENTIVE COMPLEMENTERY INTEGRATIVE APPROACHMENTS

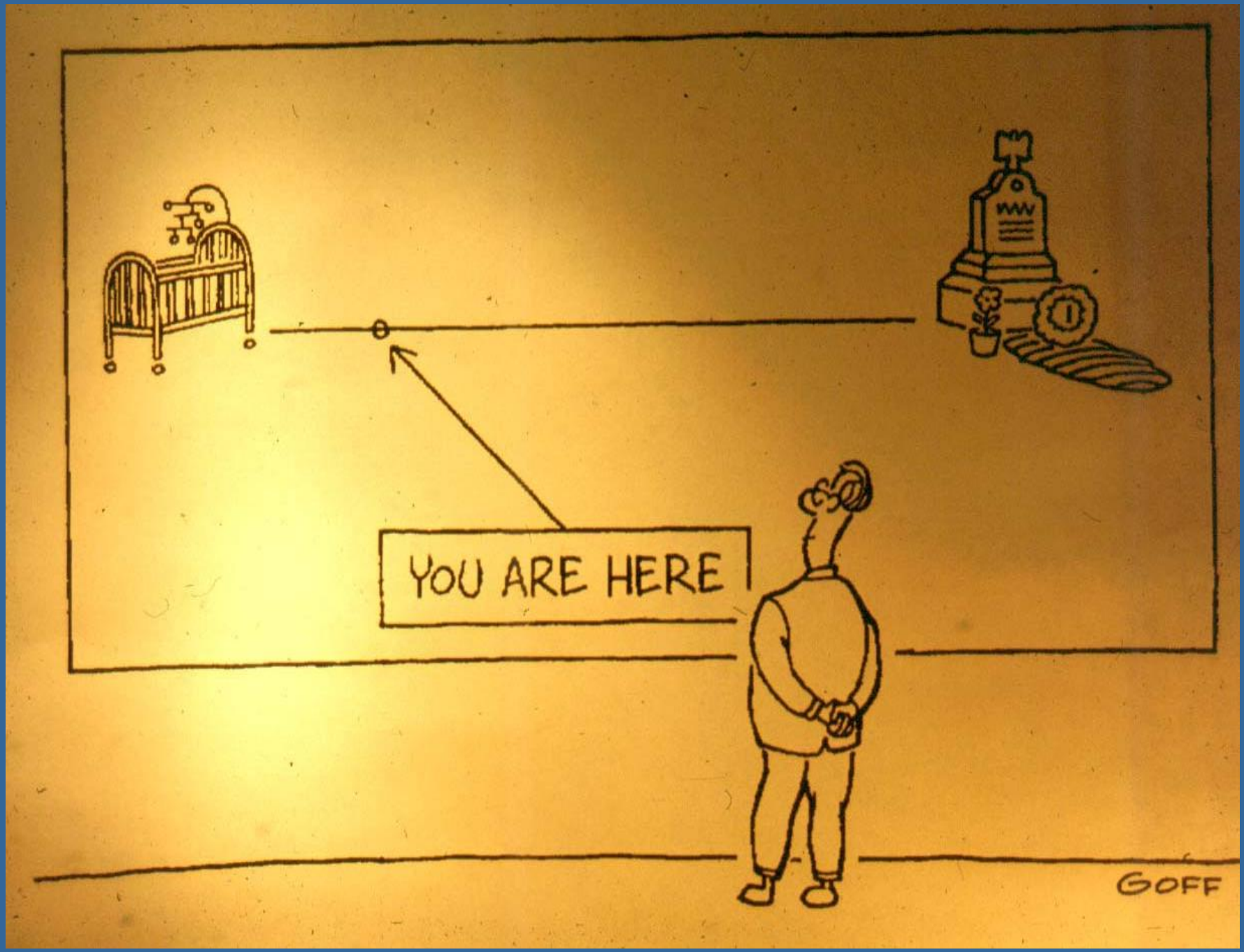
TREATMENT

STEM CELL TECH, BIOCHIPS, SELF-TISSUE GROWN TRANSPLANTS, GENE THERAPY, OTHER BIOMED TECH.

REJUVENATION




Farmaconutrigenomics
Bioengineering
Bioinformatics
Geriatrics
Metabolism
Damage
Pathology (Ageing)
Cellularbiology
Farmacogenomics
Farmacoproteomics
Biogerontology


YOU ARE HERE
GOFF

Why do some people age accelerated, some not?

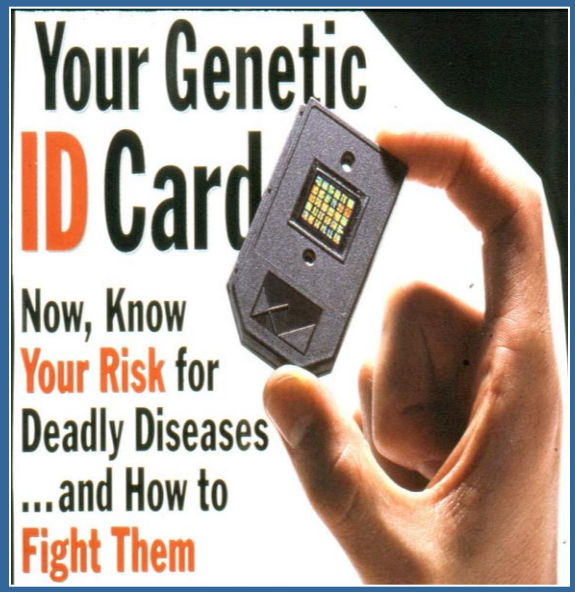
Centenarians as a model for healthy aging

C. Franceschi*†‡[1] and M. Bonafè*

*Department of Experimental Pathology, University of Bologna, Bologna, Italy, †Interdepartmental Centre "L. Galvani" for the Study of Biocomplexity, University of Bologna, Bologna, Italy, and ‡Department of Gerontological Research, Italian National Research Centre on Aging (INRCA), Ancona, Italy

Abstract

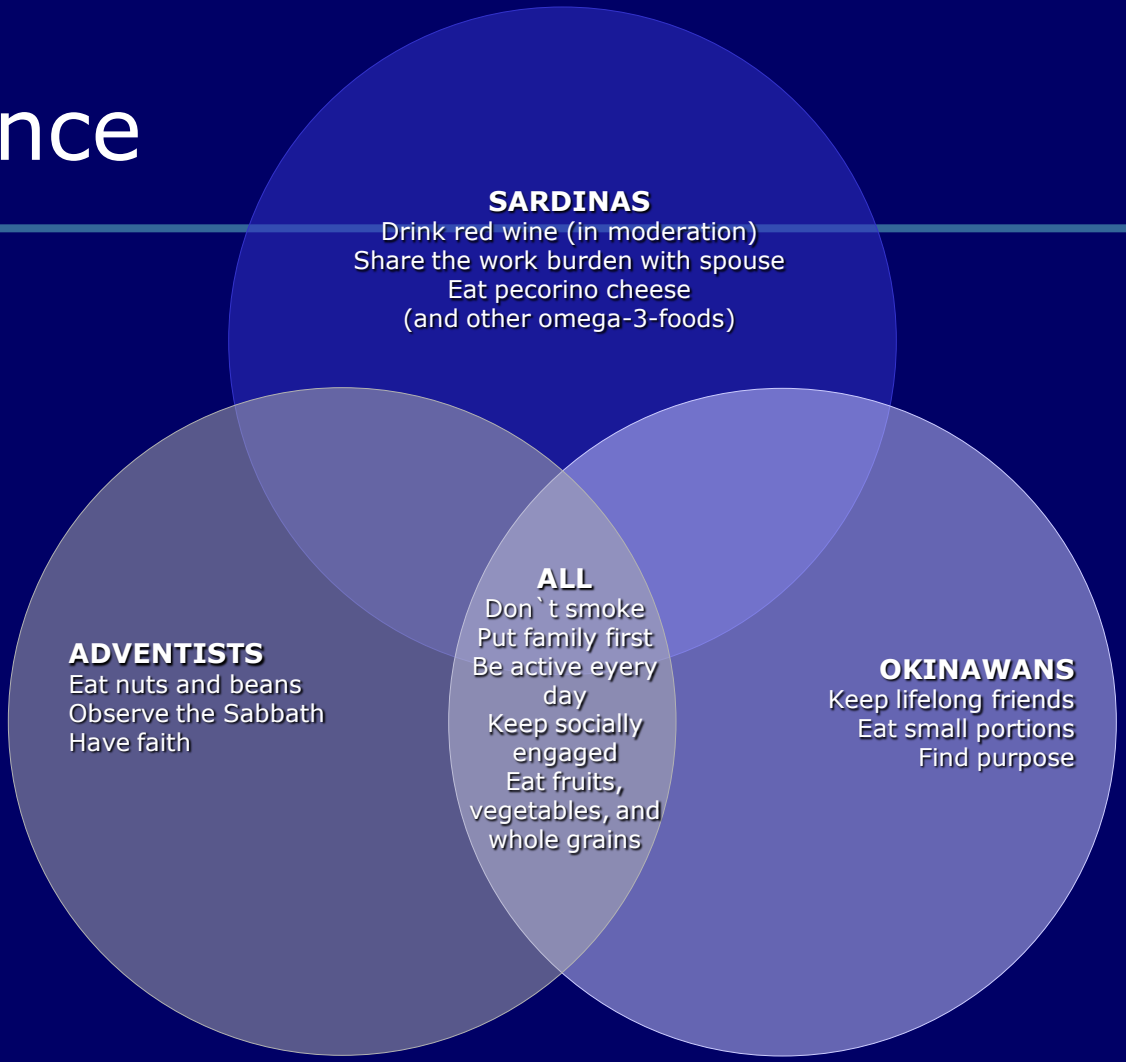
For over 10 years we have studied centenarians as a model to address the biological basis of aging and longevity, with particular attention to immunology and genetics. The most important findings can be summarized as follows. (i) Human immunosenescence represents a complex remodelling, whereby clonotypical immunity deteriorates, while ancestral, innate immunity is largely preserved. (ii) Continuous exposure to antigens causes a lifelong, chronic antigenic stress, which is responsible, together with the involution of the thymus, for the accumulation of memory/effector T cells and the exhaustion of naïve



Biochemical Society Transactions (2003) Volume 31, part 2

Experience

National Geographic, 11/05



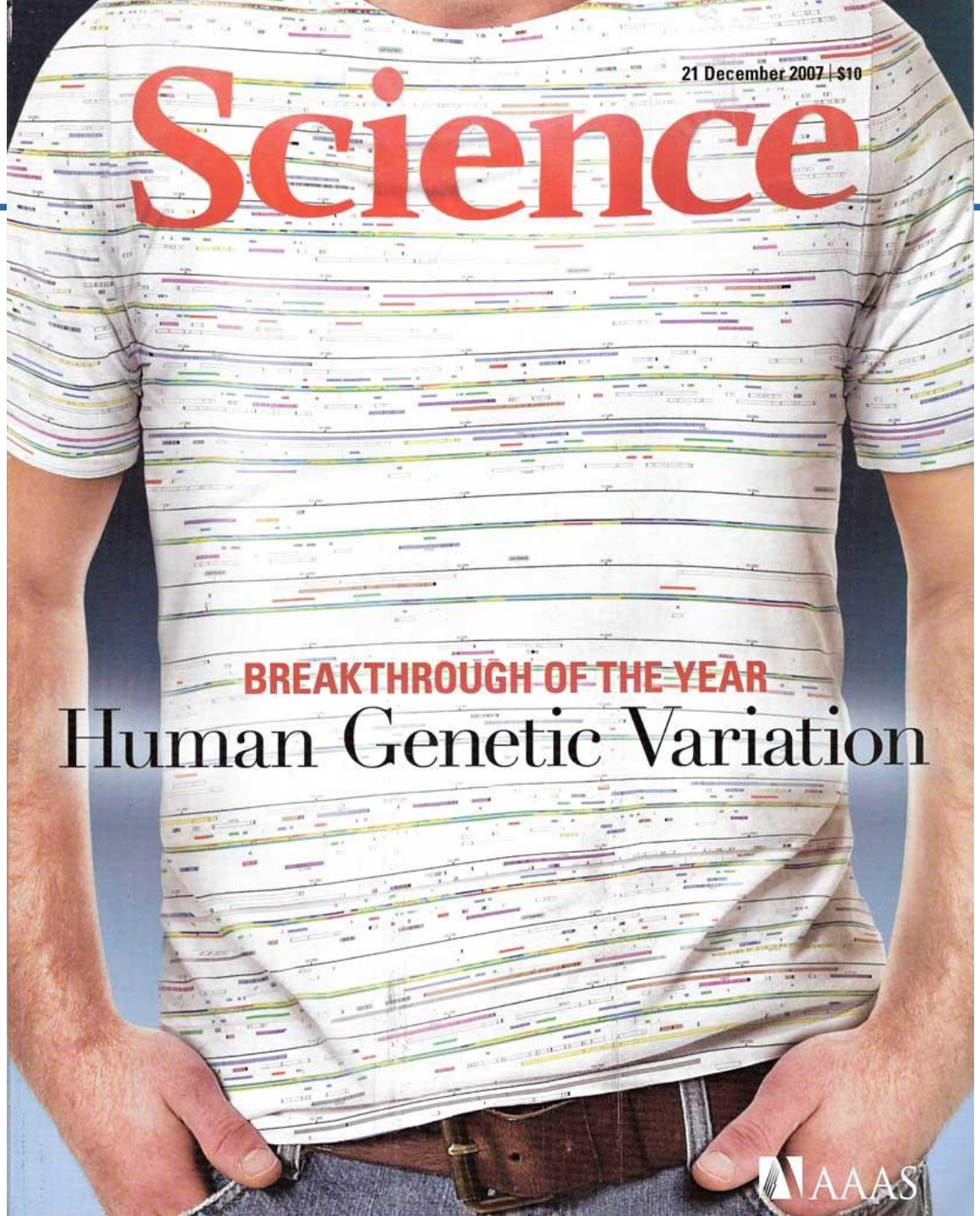
HOW TO LIVE LONGER

Super seniors in the three widely separated regions share a number of the key habits, despite many differences in backgrounds and beliefs.

Common Gene polymorphisms

National Geographic, 11/05

Long life- short life: what do your genes tell ?


Science
21 December 2007 | $10
BREAKTHROUGH OF THE YEAR
Human Genetic Variation
AAAS

AGE MANAGEMENT

STRESS MANAGEMENT

GENETICS

WEIGHT MANAGEMENT

Control of Cellular Metabolism

Control of Cellular Stressors

Nutrition
Excersize

Cognitive Training

Nutraceuticals
Mitochondrial Bioenergetics
Trace elements
Vitamins, antioxidants

AGING

ANTI-AGING

RESEARCH

Pub Med:
Aging: 244.644 publication
Anti-Aging: 4341 publication

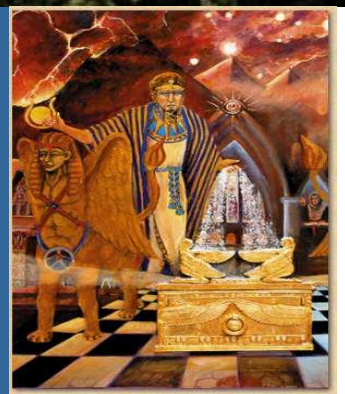
Mutations in circadian genes: late effects

Per2-/-: life span reduction,
increase in tumor incidence;

Clock/Clock: obesity, metabolic syndrome,
premature disturbances in estrous function;

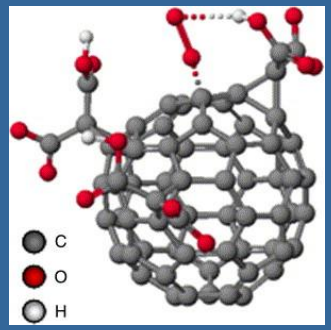
Bmal1-/-: life span reduction, increase in lipid peroxidation, cataracta, sarcopenia

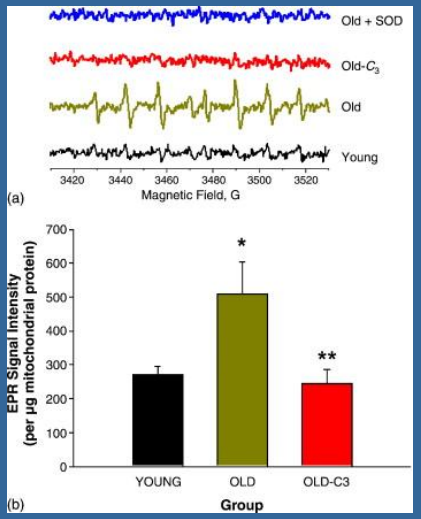
Cry1-/-Cry2-/-: no effect on life span and tumor incidence

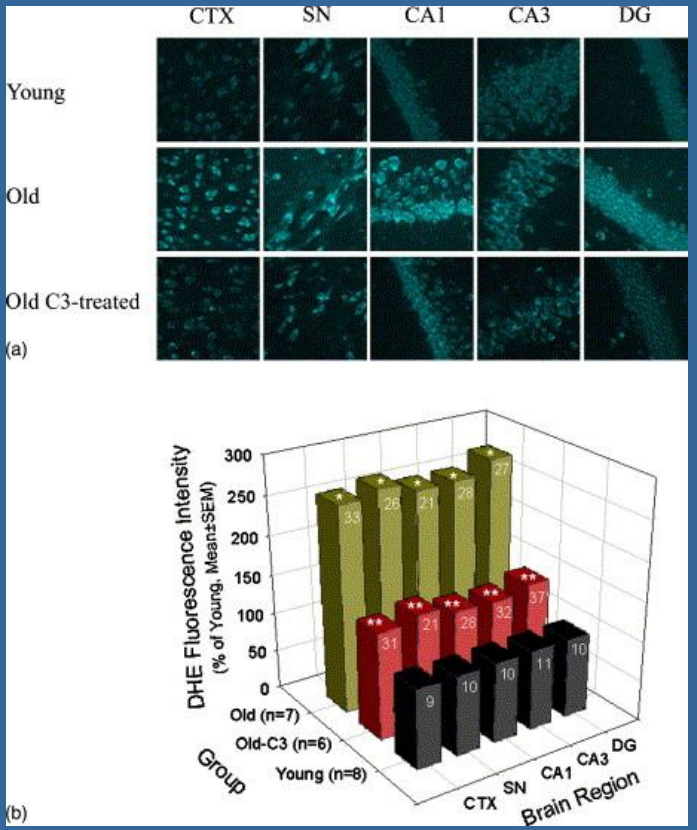


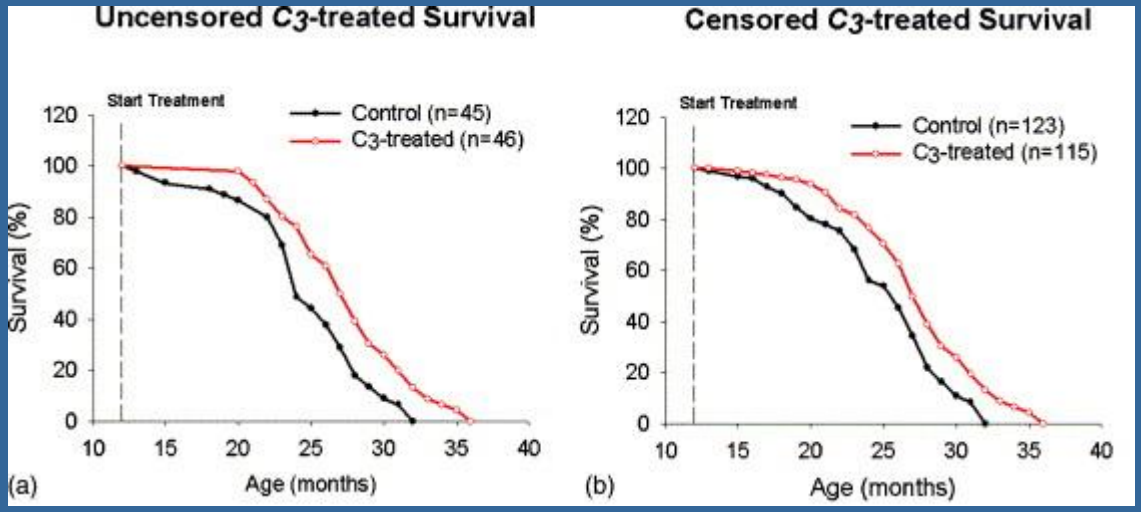


A carboxyfullerene SOD mimetic improves cognition and extends the lifespan of mice

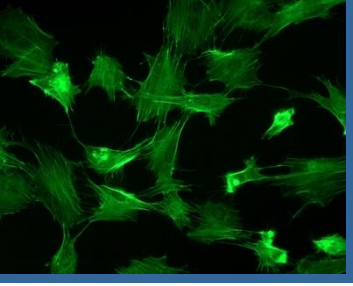




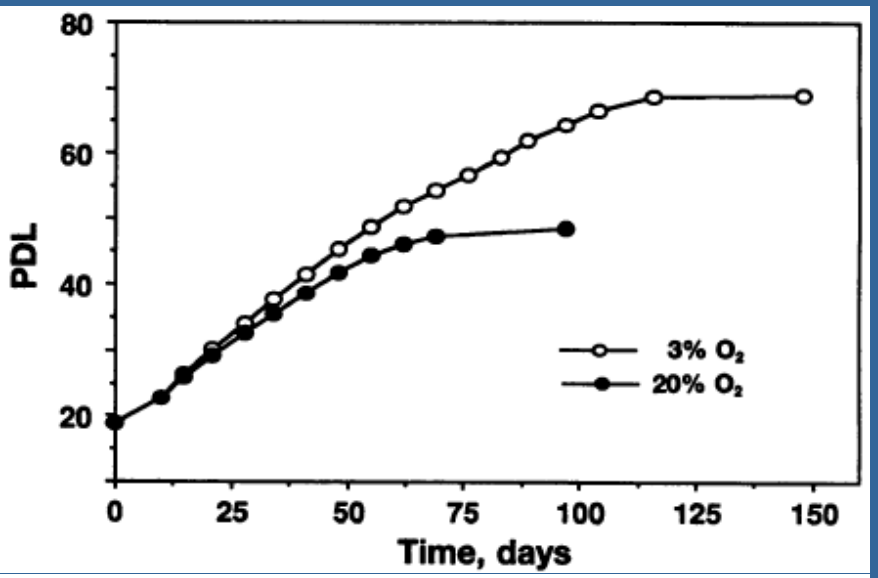


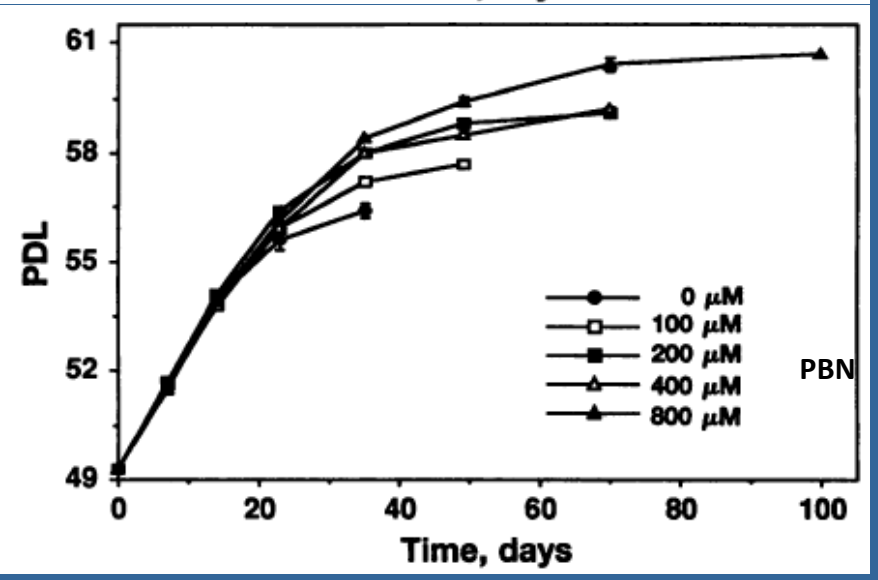


Quick et al., Neurobiol. Aging 29: 117 [2006]

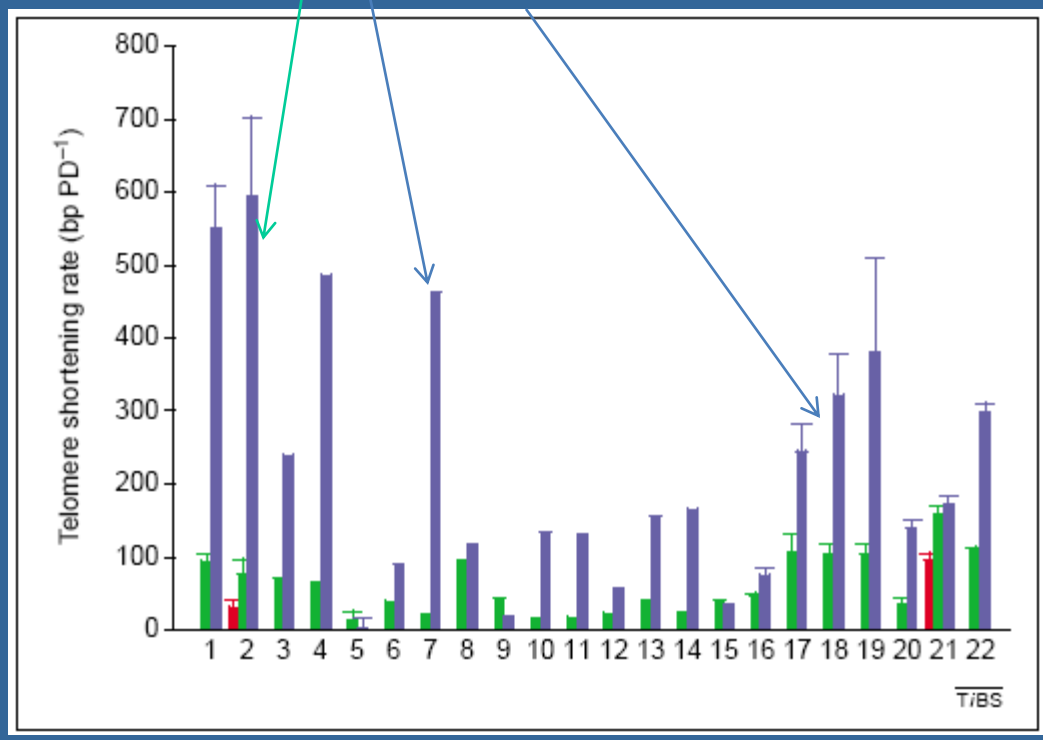


higher Hayfick limit has been observed in hypoxia or in the presence of antioxidants





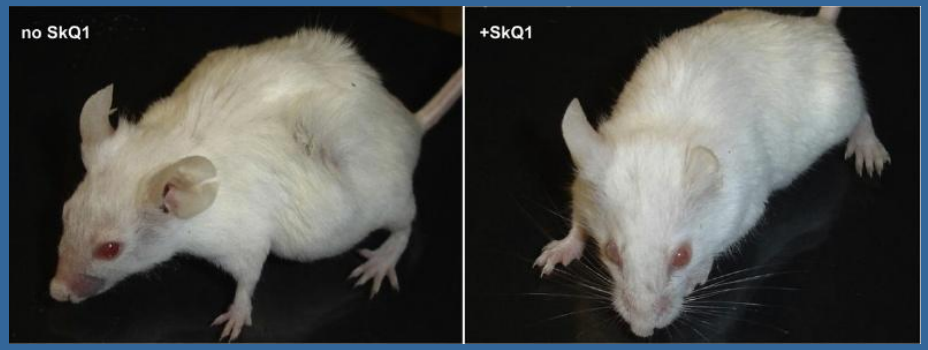
Oxidative stress shortens telomeres

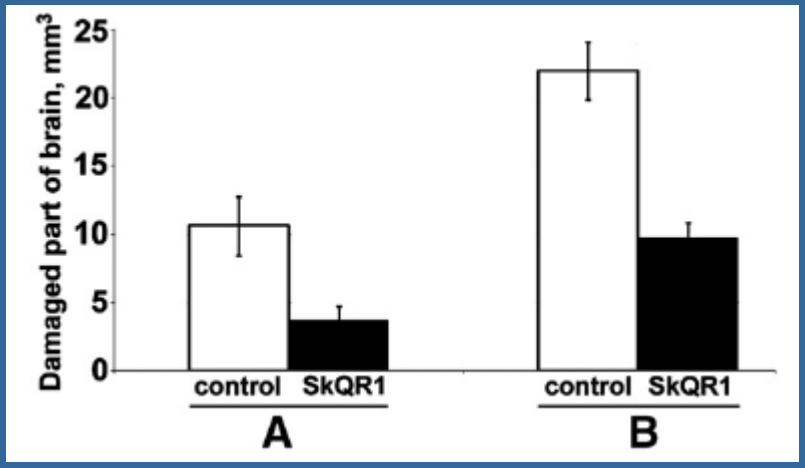


von Zglinicky, TIBS 7: 339 [2002]

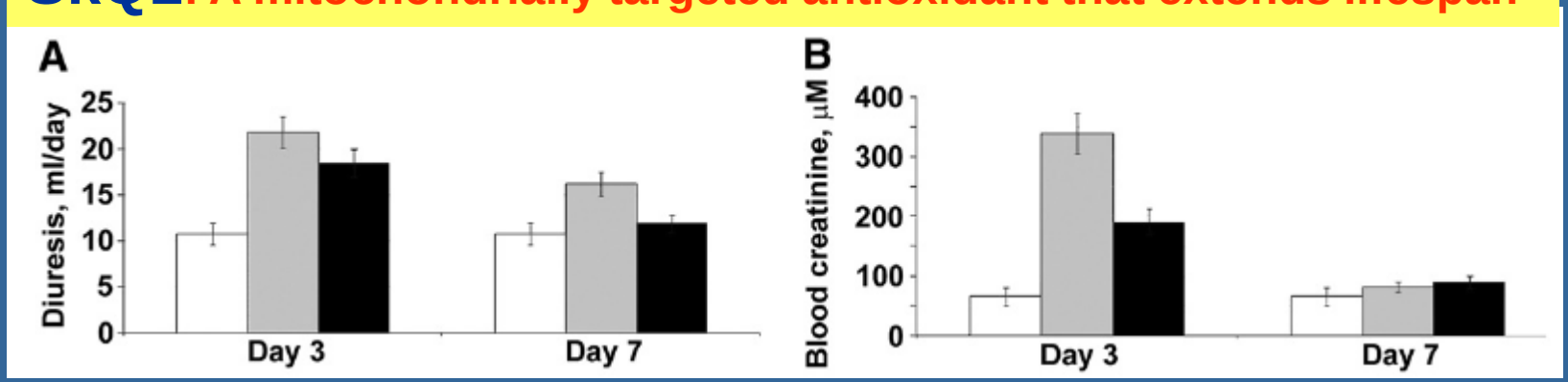
Chen et al., PNAS 92: 4337 [1995]

An attempt to prevent senescence: A mitochondrial approach





SkQ1: A mitochondrially targeted antioxidant that extends lifespan



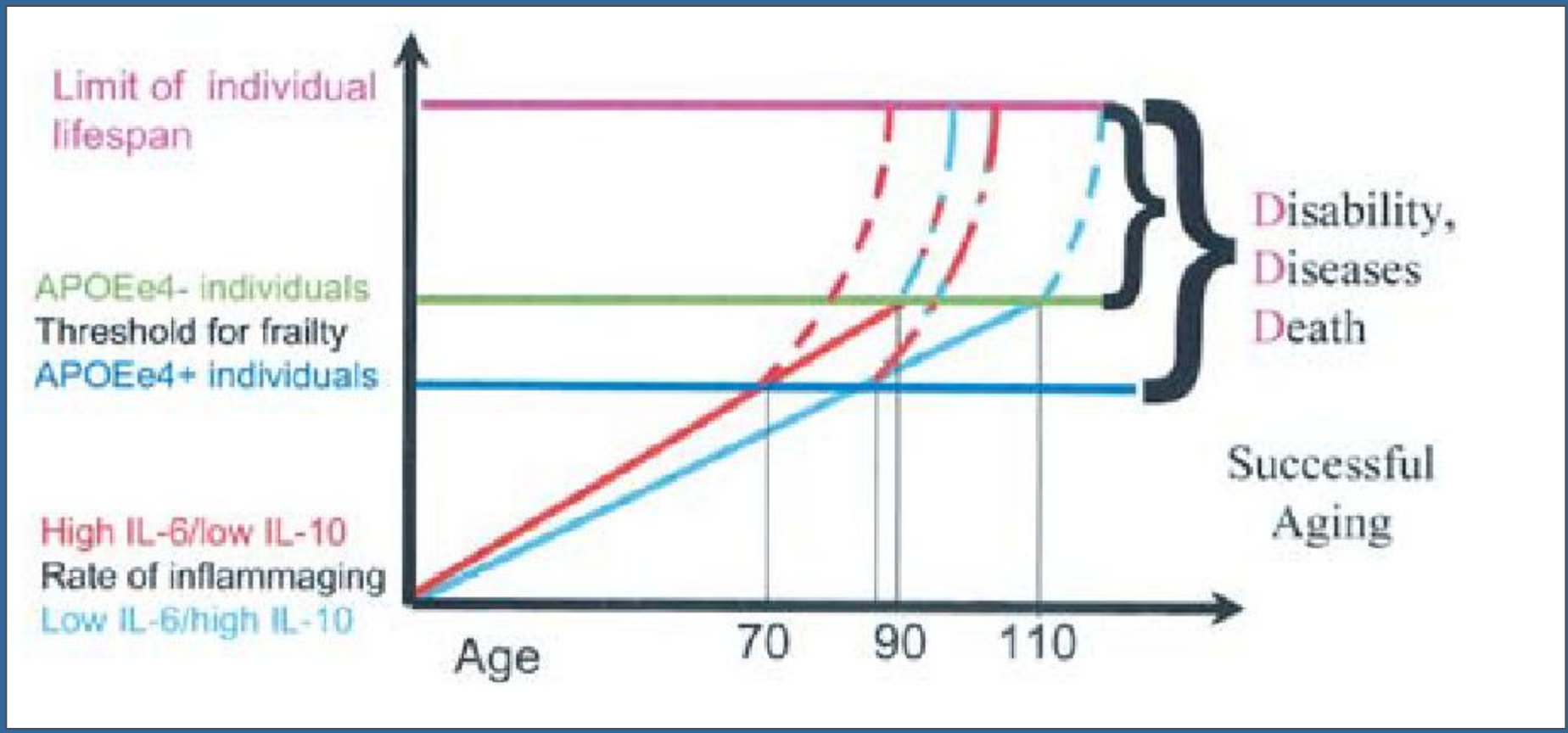
Therapeutic effect of instillations of Vetomitin (drops of SkQ1) on retinopathies

Animal species	Number of animals					
	Before treatment			After treatment		
	Blind	Partial loss of vision	Total	Vision was returned to blind animal	Vision was improved	Vision was not improved
Dog	58	19	77	46	19	12
Cat	27	9	36	17	5	14
Horse	4	18	22	4	18	0
Total	89	46	135	67	42	26

SkQ1: protective effects on reperfusion injury, cataract and retinopathies

Skulachev et al., BBA 1787: 437 [2009]

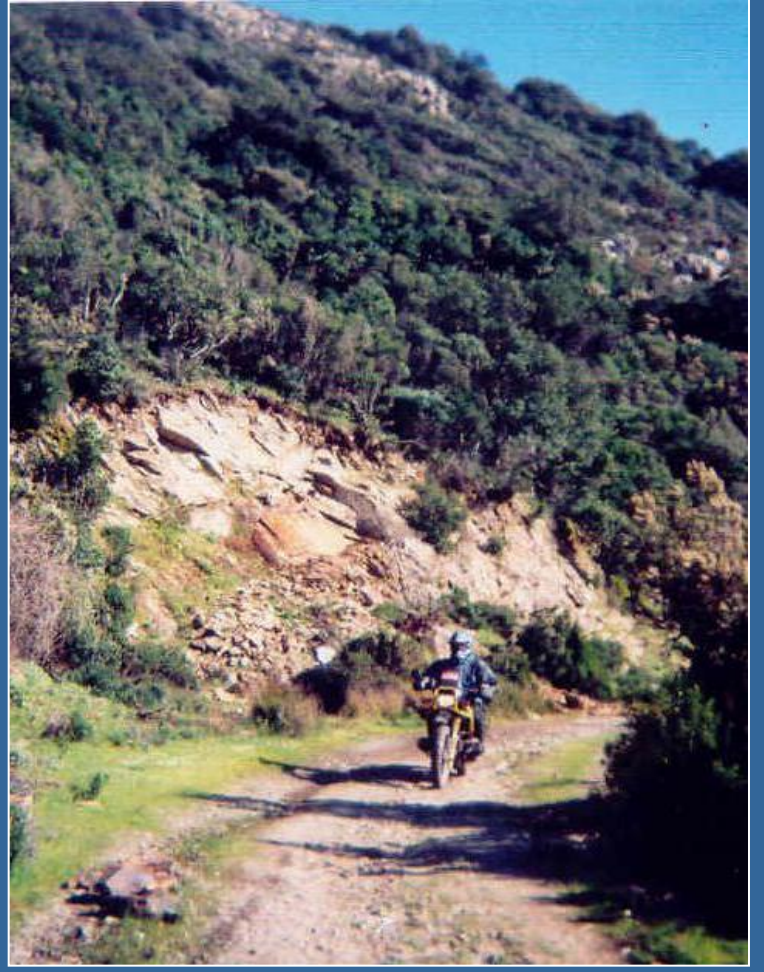
Increase of IL-6 and decrease of IL-10 leads to inflammaging and accelerated Aging



Aging Clin Exp Res. 2004 Jun;16(3):244-8.

Association between longevity and cytokine gene polymorphisms. A study in Sardinian centenarians

Pes GM Lio D Carru C, Deiana L, Baggio G, Franceschi C, Ferrucci L, Oliver F Scola L, Crivello A, Candore G, Colonna-Romano G, Caruso C.



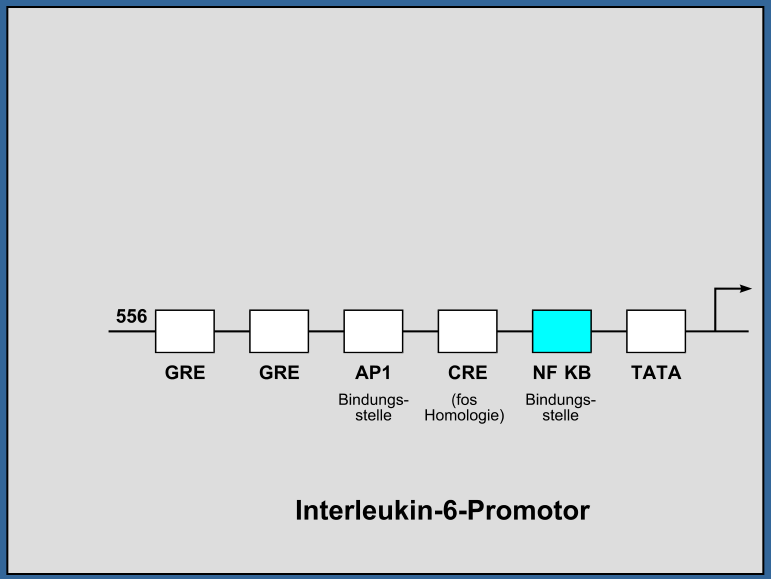
Human longevity seems to be directly correlated with optimal functioning of the immune system, suggesting that some genetic determinants of longevity reside in those polymorphisms for the immune system genes which regulate immune-inflammatory responses, in particular cytokine gene polymorphisms. The frequency of -174C single nucleotide polymorphism (SNP) in the promoter region of the interleukin (IL)-6 gene is increased in Italian male centenarians.

IL – 6 POLYMORPHISMUS
174 GG

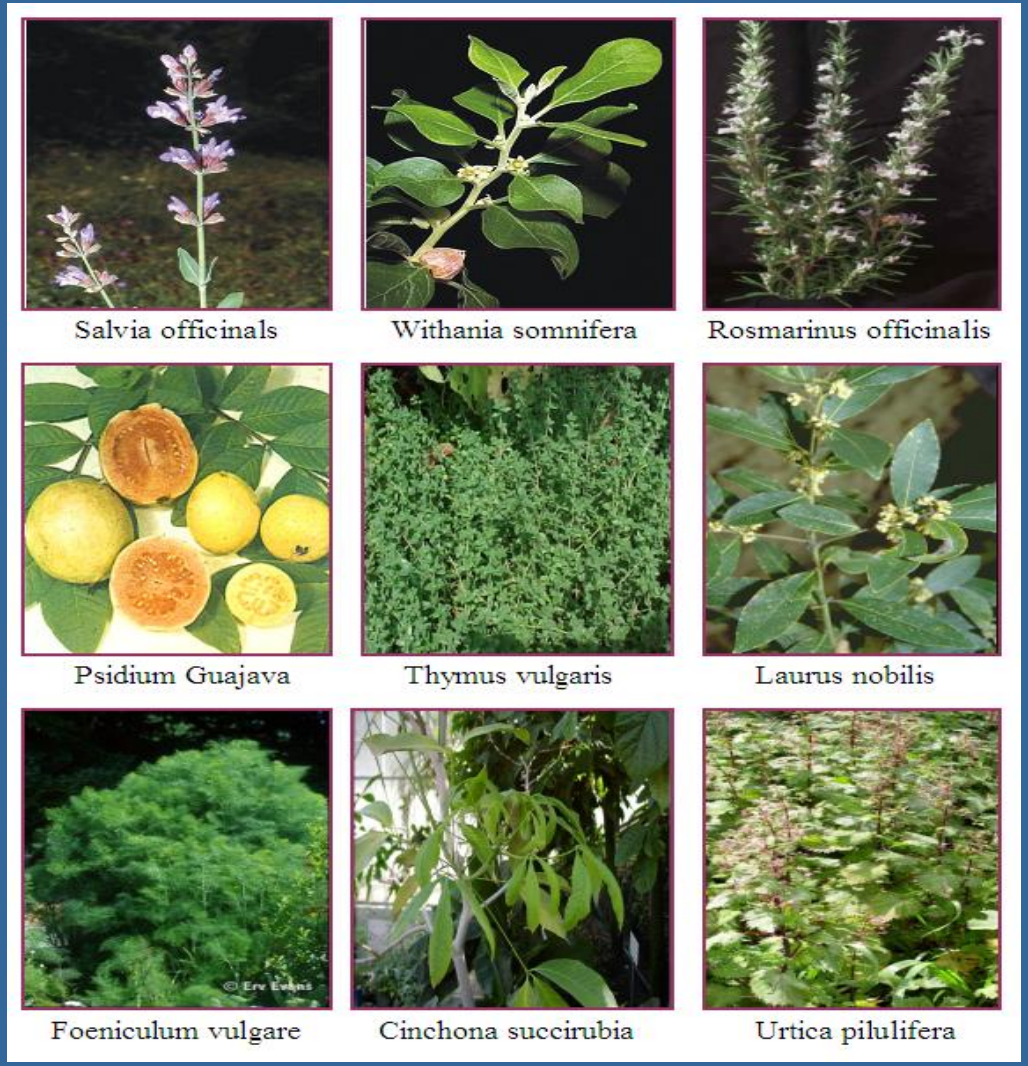
HIGH IL-6 LEVELS ARE THE MAIN PREDICTURS OF DISABILITY AND MORTALITY IN THE ELDERLY.

. Am Geriatr. Soc. 47:639-646 (1999)

increase in inflammaging (the slope of inflammaging). In this regard, we found that subjects homozygous for the IL-6 −174 GG polymorphism had higher plasma levels of IL-6 than carriers of allele C at position −174 [12]. Independent studies found that high IL-6 levels are the major predictor of disability and mortality in the elderly [18]. We also found that the IL-6 −174 GG genotype is underrepresented in centenarians. We thus considered that the IL-6 −174 genotype may be a major modulator of inflammaging. We found this phenomenon to be restricted primarily to males, suggesting that the two genders follow different trajectories to attain longevity.



Constitutional NFkB activation during aging, originated by free radical increase contributes to incerased IL-6 and inflammation→ decerased IL-2



IL6 Physiology

- Inflammation
- Immunity
- Bone metabolism
- Neural Development
- Reproduction
- Hematopoiesis

IL6 Pathophysiology

- Chronic inflammation
- Autoimmunity
- Diabetes
- Cardiovascular disease
- Ageing, frailty
- Osteoporosis
- Alzheimer
- Neoplasia, Leukemia
- Atheriosclerosis
- Rheumatoid arthritis

The Interleukin-6 inflammation pathway from cholesterol to aging – Role of statins, bisphosphonates and plant polyphenols in aging and age-related diseases

Sota Omoigui
Division of Inflammation and Pain Medicine, L.A Pain Clinic, 4019 W. Rosecrans Ave, Los Angeles, CA 90250, USA

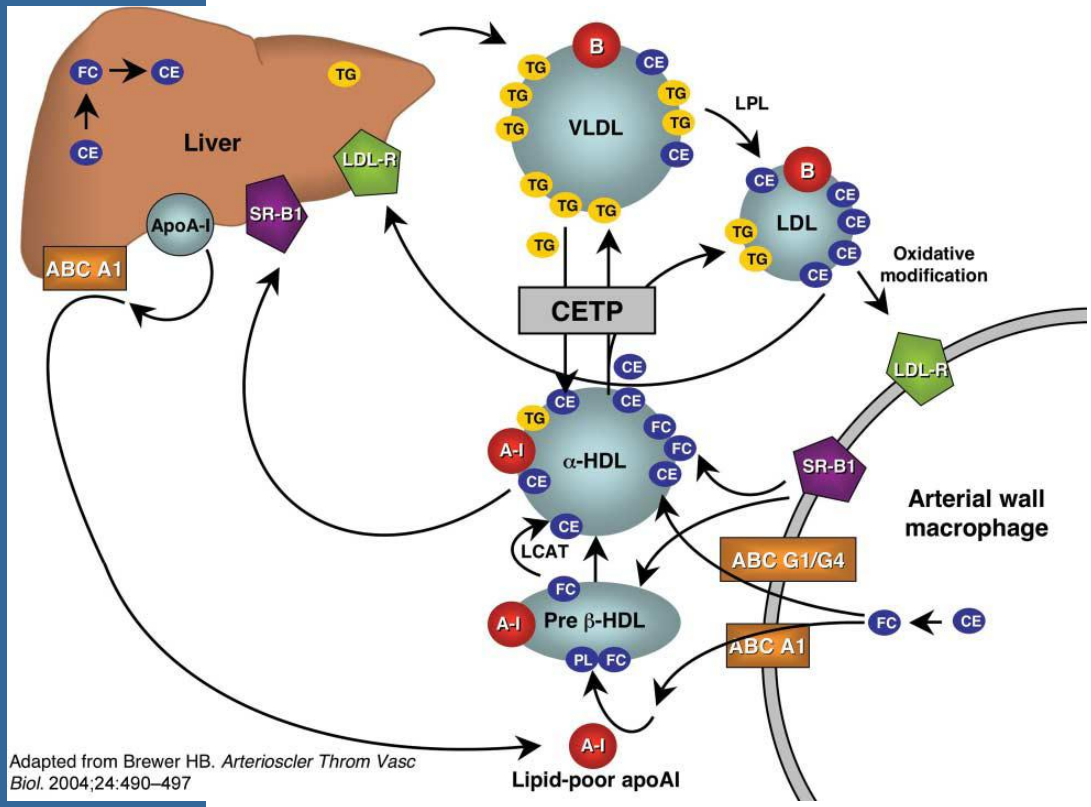
author email corresponding author email

Immunity & Ageing 2007, **4**:1 doi:10.1186/1742-4933-4-1

The electronic version of this article is the complete one and can be found online at:
http://www.immunityageing.com/content/4/1/1

Cholesteryl ester transfer protein (CETP) I405V polymorphism and longevity in Italian centenarians

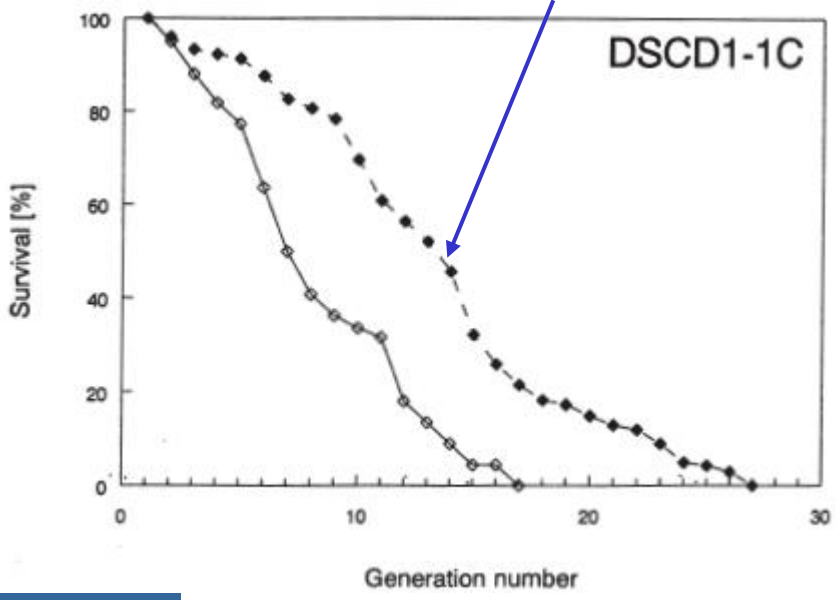
CELLINI Elena ; NACMIAS Benedetta ; OLIVIERI Fabiola ; ORTENZI Luigi ; TEDDE Andrea
BAGNOLI Silvia , PETRUZZI Concetta , FRANCESCHI Claudio SORBI Sandro



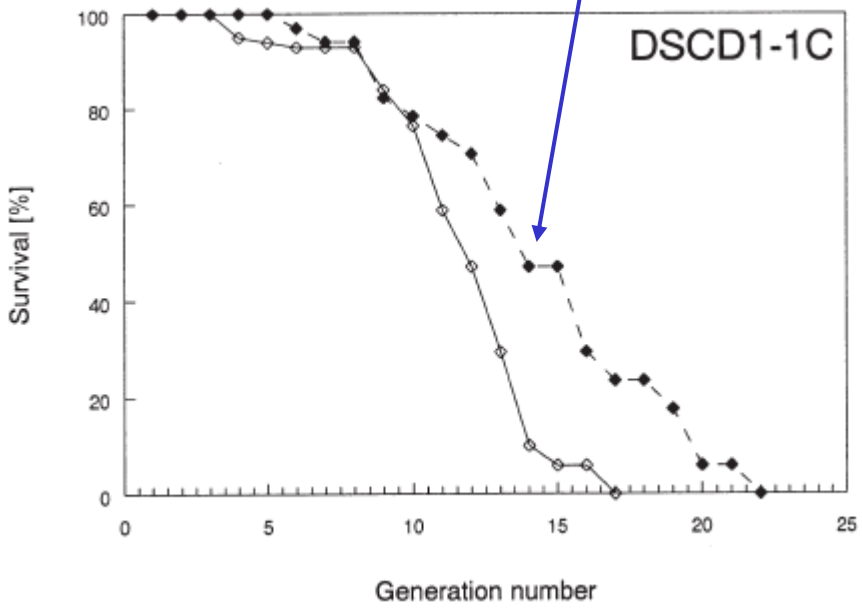
- **A common polymorphism (1405V) in exon 14 of the cholesteryl ester transfer protein (CETP) gene has been recently associated to healthy aging in Ashkenazi Jewish.**

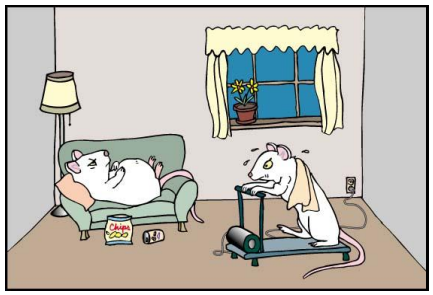
Hormesis: stress can stimulate defence and repair mechanisms and prolong lifespan

Repetitive heat shock



Repetitive osmotic stress





J. Vina: "Exercise is the best antioxidant"

Swieciło et al., Acta Biochim. Pol. 47: 355 [2000]

Critical Reviews in Toxicology, 38:629–631, 2008

ISSN: 1040-8444 print / 1547-6898 online
DOI: 10.1080/10408440802026372

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healthcare

Peptides and Hormesis

Abba J. Kastin and Weihong Pan
Pennington Biomedical Research Center, Baton Rouge, Louisiana, USA

Biology is replete with examples of hormesis, the term introduced and developed by Calabrese. The corresponding concept in the field of peptide research has been characterized as the inverted U-shaped dose-response relationship. The articles by Calabrese in this issue summarize the notable progress occurring in the past three decades. In contrast to the skepticism encountered when we introduced this concept for peptides in the early 1970s, hormesis is now becoming recognized as characteristic of many actions of these small proteins. Calabrese is performing a considerable service by his strong advocacy and promotion of the concept to a more general readership. Hopefully, hormesis will be routinely considered in the design of research projects and the discovery of pharmaceutical agents.

Keywords bell-shaped, dose response, hormesis, inverted-U, MIF-1, MSH, peptides

BJCP British Journal of Clinical Pharmacology

Hormesis and medicine

Edward J. Calabrese

Department of Public Health, Environmental Health Sciences, Morrill I, N344, University of Massachusetts, Amherst, MA 01003, USA

DOI:10.1111/j.1365-2125.2008.03243.x

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Keywords
biphasic, dose–response, history of medicine, hormetic, hormesis, J-shaped, U-shaped, anxiolytic, seizure, memory, stroke, prion, prostate, biophosphonates, statins, erectile dysfunction, protein folding, retinal detachment, tumor cell proliferation

Received
25 March 2008
Accepted
3 June 2008

Evidence is presented which supports the conclusion that the hormetic dose–response model is the most common and fundamental in the biological and biomedical sciences, being highly generalizable across biological model, endpoint measured and chemical class and physical agent. The paper provides a broad spectrum of applications of the hormesis concept for clinical medicine including anxiety, seizure, memory, stroke, cancer chemotherapy, dermatological processes such as hair growth, osteoporosis, ocular diseases, including retinal detachment, statin effects on cardiovascular function and tumour development, benign prostate enlargement, male sexual behaviours/dysfunctions, and prion diseases.

Human & Experimental Toxicology (2008) **27:** 155–162
http://het.sagepub.com

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ScienceDirect
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ELSEVIER

Genes and environment — Striking the fine balance between sophisticated biomonitoring and true functional environmental genomics

Christian E.W. Steinberg[a,*], Stephen R. Stürzenbaum[b], Ralph Menzel[a]

[a]Humboldt University, Institute of Biology, Laboratory of Freshwater & Stress Ecology, Arboretum, Späthstraße 80/81, 12437 Berlin, Germany
[b]School of Biomedical & Health Sciences, Pharmaceutical Sciences Division, King's College London, 150 Stamford Street, London SE1 9NH, United Kingdom

ARTICLE DATA

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ABSTRACT

This article provides an overview how the application of the gene profiling (mainly via microarray technology) can be used in different organisms to address issues of environmental importance. Only recently, environmental sciences, including ecotoxicology, and molecular biology have started to mutually fertilize each other. This

Critical Reviews in Toxicology, 38:641–644, 2008

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DOI: 10.1080/10408440802026422

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Hormesis, Adaptation, and the Sandpile Model

Martha Stark
Faculty, Continuing Education Program, Beth Israel Deaconess Medical Center, and Faculty, Center for Psychoanalytic Studies, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

BELLE Article:

Hormesis and disease resistance: activation of cellular stress response pathways

Mark P Mattson*

Laboratory of Neurosciences, National Institute on Aging Intramural Research Program, Baltimore, MD, USA

JAMA®

Online article and related content current as of November 1, 2008.

Effect of 6-Month Calorie Restriction on Biomarkers of Longevity, Metabolic Adaptation, and Oxidative Stress in Overweight Individuals: A Randomized Controlled Trial

Leonie K. Heilbronn; Lilian de Jonge; Madlyn I. Frisard; et al.

JAMA. 2006;295(13):1539-1548 (doi:10.1001/jama.295.13.1539)

http://jama.ama-assn.org/cgi/content/full/295/13/1539

Design, Setting, and Participants Randomized controlled trial of healthy, sedentary men and women (N = 48) conducted between March 2002 and August 2004 at a research center in Baton Rouge, La.

Intervention Participants were randomized to 1 of 4 groups for 6 months: control (weight maintenance diet); calorie restriction (25% calorie restriction of baseline energy requirements); calorie restriction with exercise (12.5% calorie restriction plus 12.5% increase in energy expenditure by structured exercise); very low-calorie diet (890 kcal/d until 15% weight reduction, followed by a weight maintenance diet).

Main Outcome Measures Body composition; dehydroepiandrosterone sulfate (DHEAS), glucose, and insulin levels; protein carbonyls; DNA damage; 24-hour energy expenditure; and core body temperature.

Conclusions Our findings suggest that 2 biomarkers of longevity (fasting insulin level and body temperature) are decreased by prolonged calorie restriction in humans and support the theory that metabolic rate is reduced beyond the level expected from reduced metabolic body mass. Studies of longer duration are required to determine if calorie restriction attenuates the aging process in

The beneficial effects of a CR diet partly related to reduced oxidant intake, rather than decreased energy intake

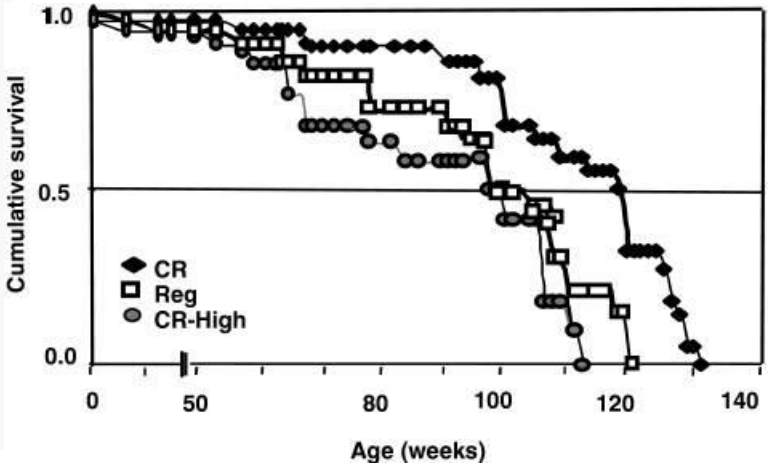
Am J Pathol. 2008 August; 173(2): 327–336.
doi: 10.2353/ajpath.2008.080152.
PMCID: PMC2475771

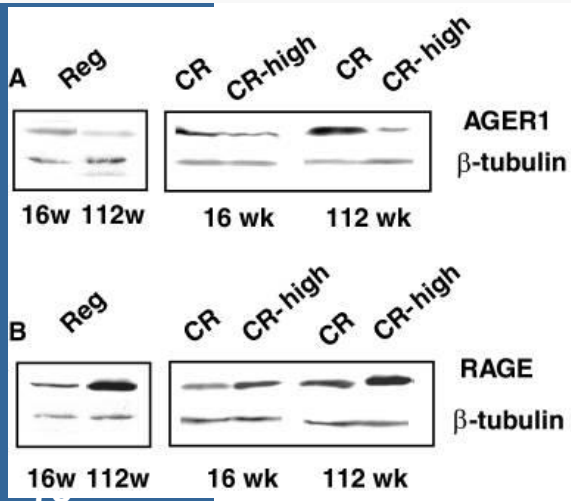
Oral Glycotoxins Determine the Effects of Calorie Restriction on Oxidant Stress, Age-Related Diseases, and Lifespan

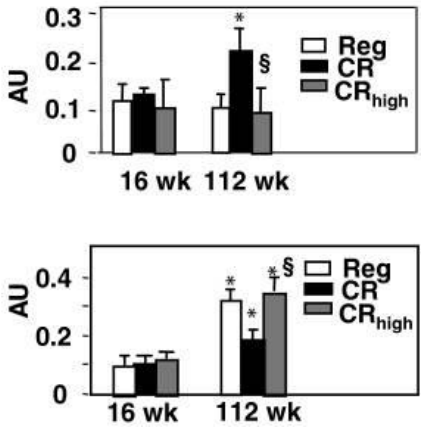
Weijing Cai,* John C. He,† Li Zhu,* Xue Chen,* Feng Zheng,* Gary E. Striker,†‡ and Helen Vlassara*

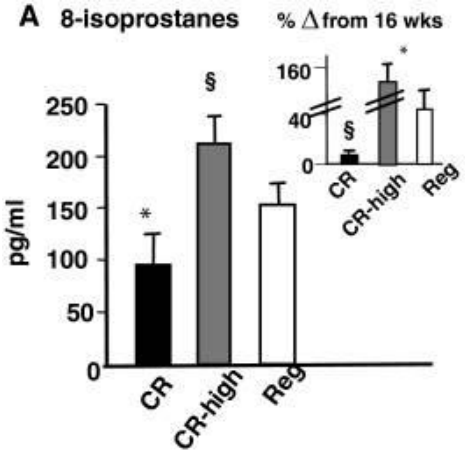
From the Department of Geriatrics,* Division of Experimental Diabetes and Aging, and the Department of Medicine,† Division of Nephrology, Mount Sinai School of Medicine, New York, New York; and the Departments of Medicine and Surgery,‡ Miller School of Medicine, University of Miami, Miami, Florida

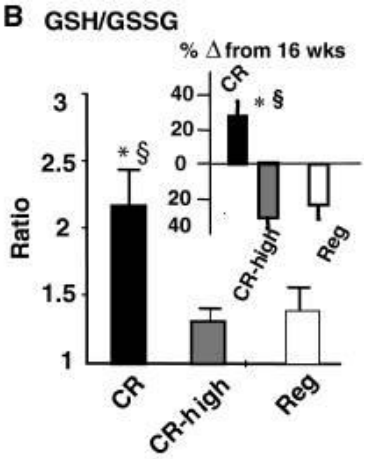
Accepted April 24, 2008.









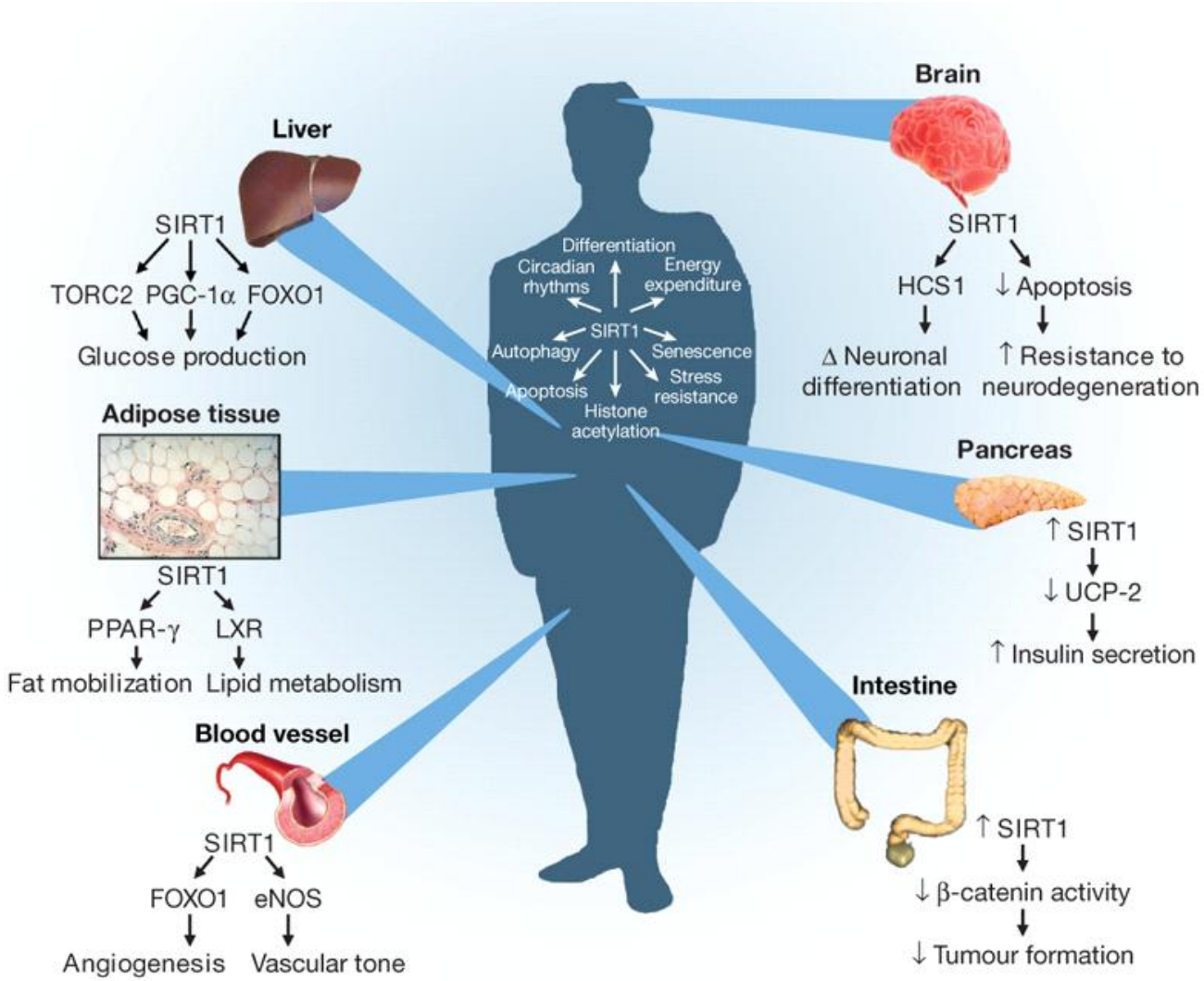


Sirtuins are NAD+-dependent protein deacetylases that are broadly conserved from bacteria to humans.

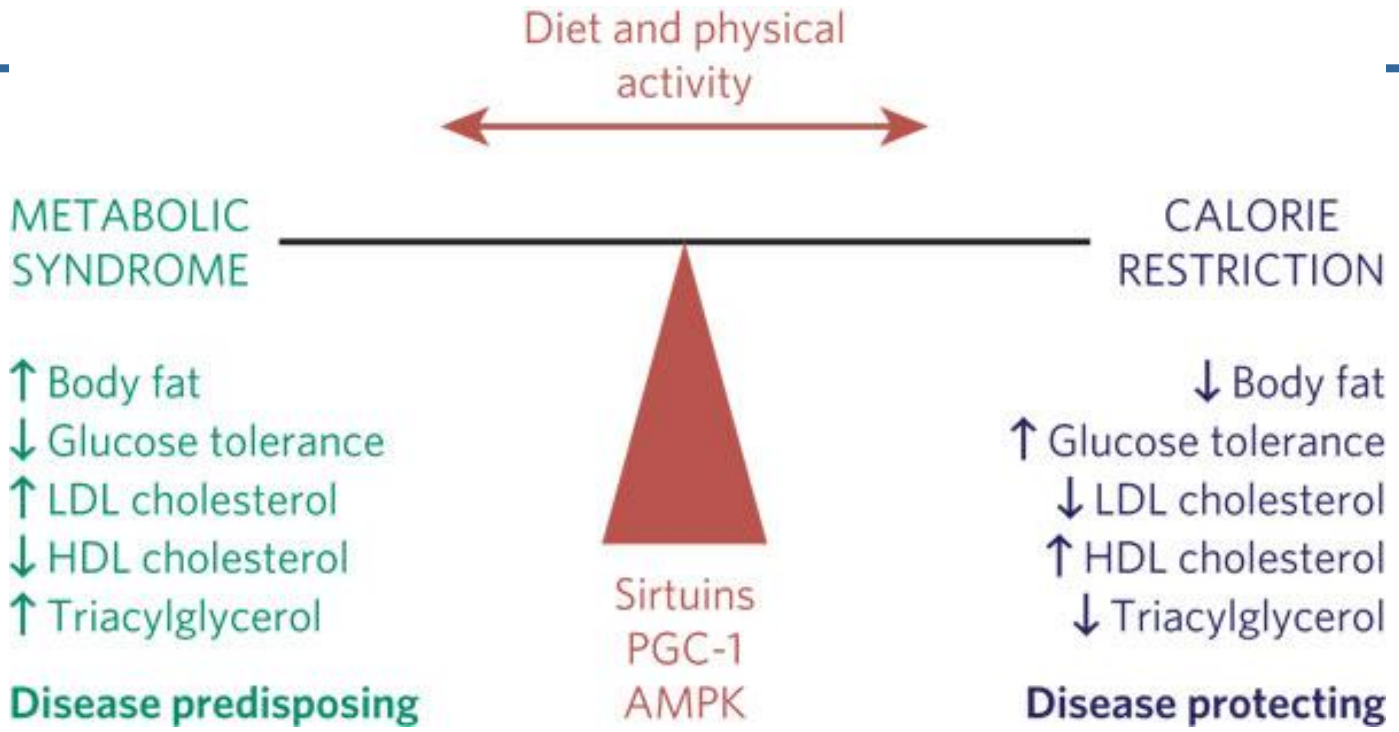
Because sirtuins extend the lifespan of yeast, worms and flies, much attention has been paid to their mammalian homologues

Stvolinsky et al., 2010

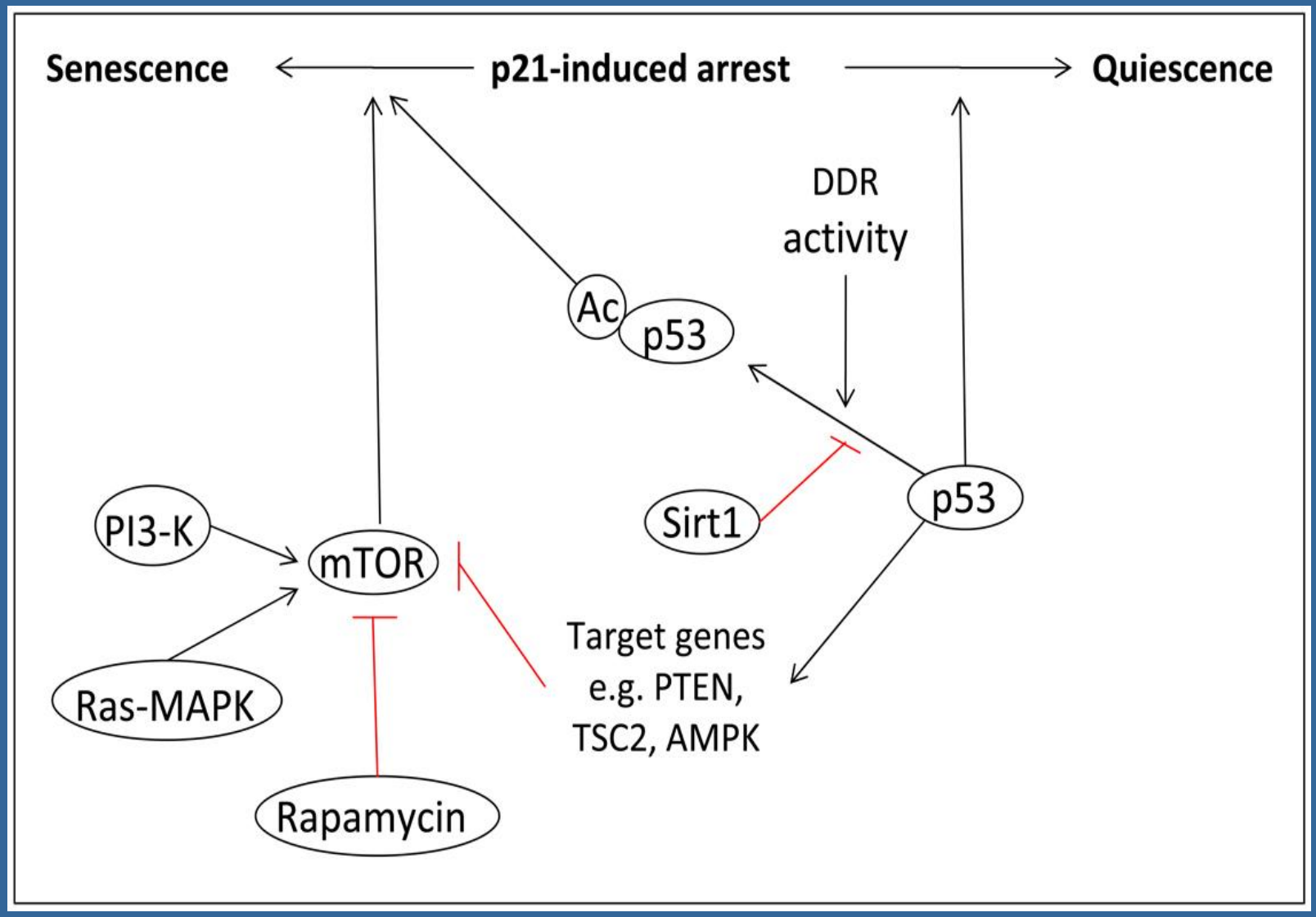
Horio et al., 2011

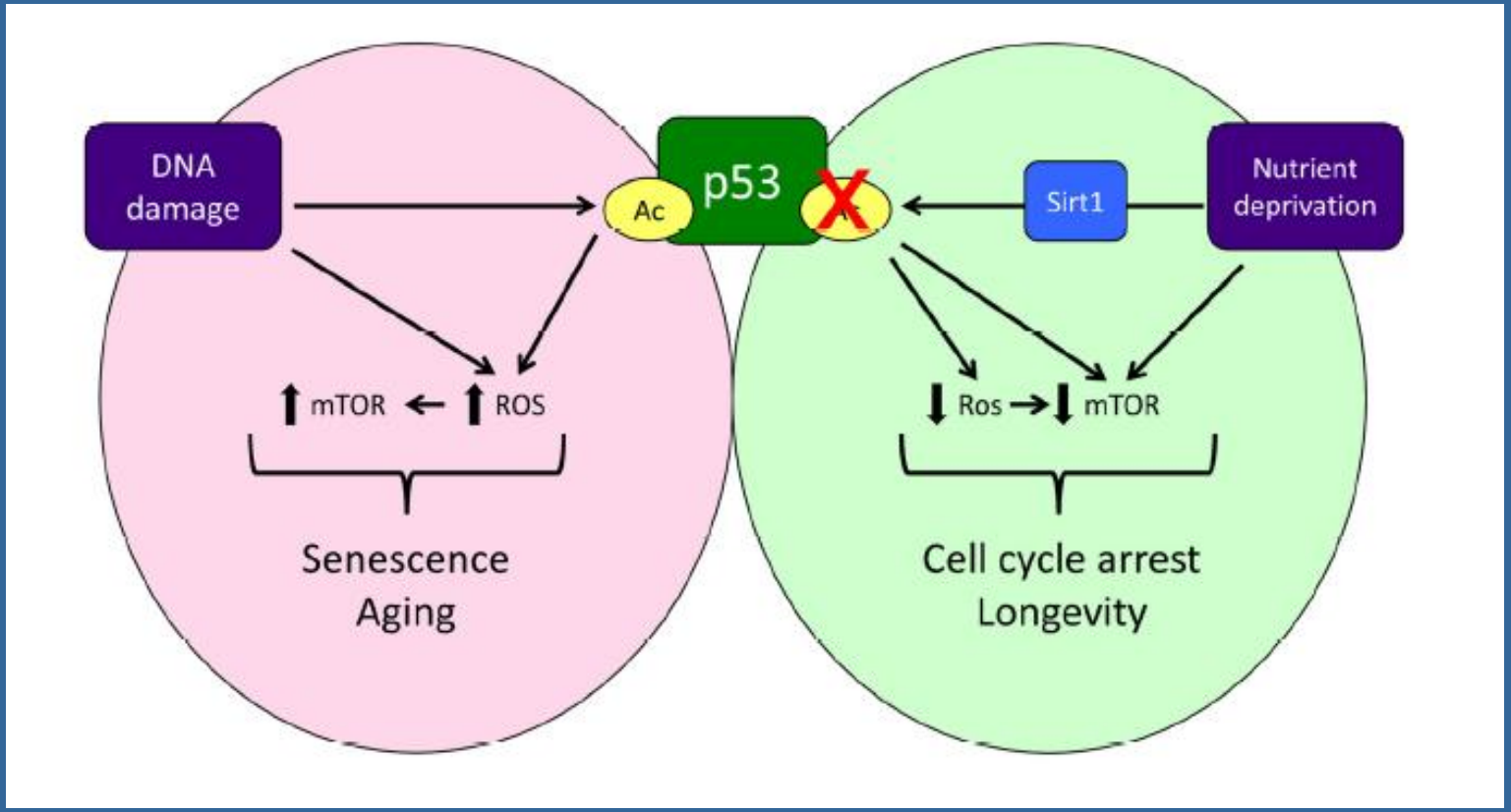


Stvolinsky et al., 2010



resveratrol, increases the catalytic (deacetylase) activity of SIRT-1, mimics the effects of calorie restriction


Senescence
p21-induced arrest
Quiescence
DDR
activity
Ac
p53
PI3-K
mTOR
Sirt1
p53
Ras-MAPK
Target genes
e.g. PTEN,
TSC2, AMPK
Rapamycin


DNA damage
p53
Ac
Sirt1
Nutrient deprivation
mTOR
ROS
Ros
mTOR
Senescence
Aging
Cell cycle arrest
Longevity

Autophagy as an anti-aging mechanism

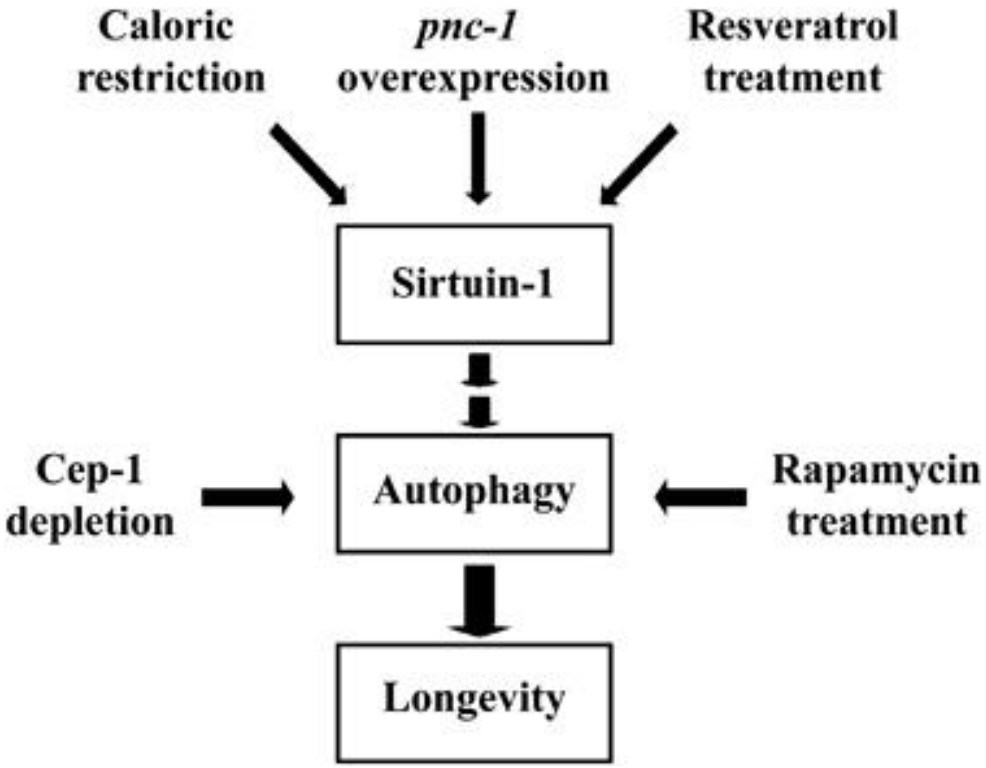
Pharmacological or genetic manipulations designed to prolong lifespan induce autophagy in multiple model organisms, including yeast, nematodes and flies, and the inhibition of autophagy often (always?) prevents longevity extension in such settings. This applies to lifespan extension induced by caloric restriction, genetic or pharmacological activation of Sirtuin 1, inhibition of the mammalian target of rapamycin (mTOR) with rapamycin, and administration of spermidine, a histone acetylase inhibitor [3,4,81,104-107]. Among these stimuli, there is circumstantial evidence that Sirtuin 1 (whose activation occurs during and is necessary for starvation- and resveratrol-induced autophagy) acts in a hormetic fashion. One of the best-known systems of hormesis is ischemic preconditioning (IPC), whereby short episodes of ischemia protect the brain against a later, more severe reduction in oxygen and nutrient supply. In this system, the administration of resveratrol can mimic IPC, and both resveratrol and IPC induce similar changes in the acetylproteome of the brain [53].

Aging (Albany NY). 2011 Sep 8. [Epub ahead of print]

Hormesis, cell death and aging.

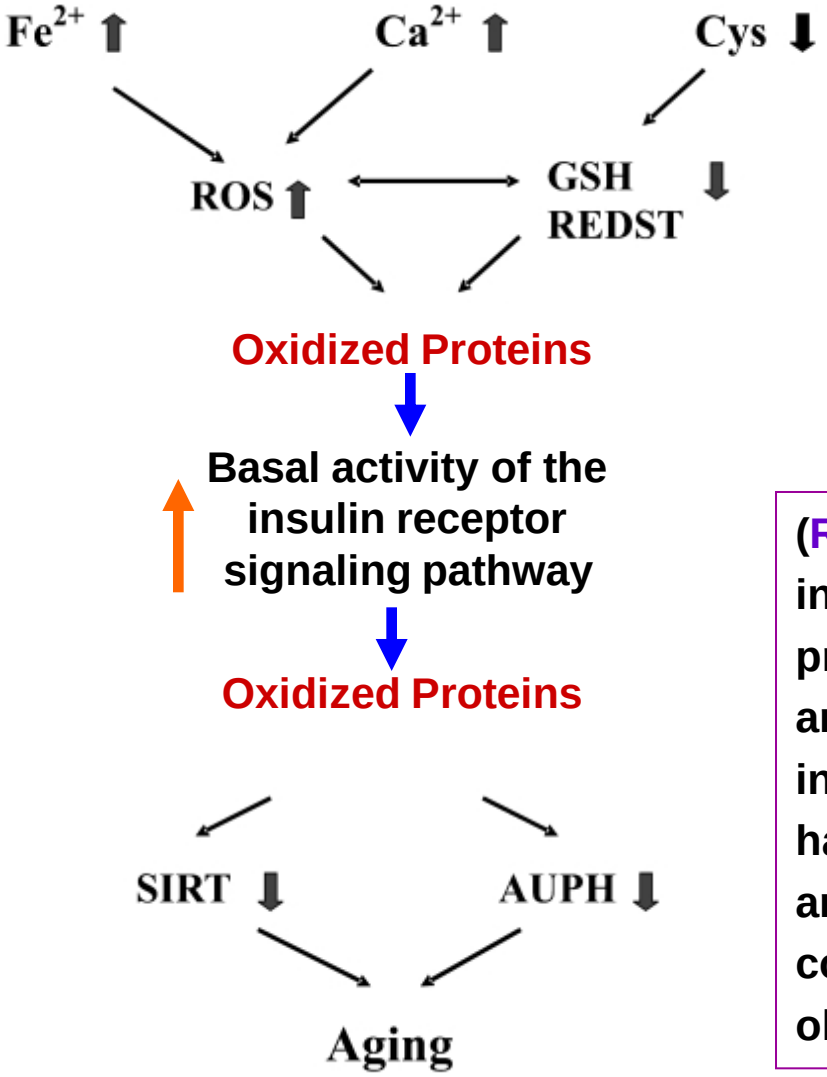
Martins I, Galluzzi L, Kroemer G.

INSERM, U848, 94805 Villejuif, France.



We gain weight and Insulin

Oxidative pathomechanisms of neurodegeneration in cognitive aging



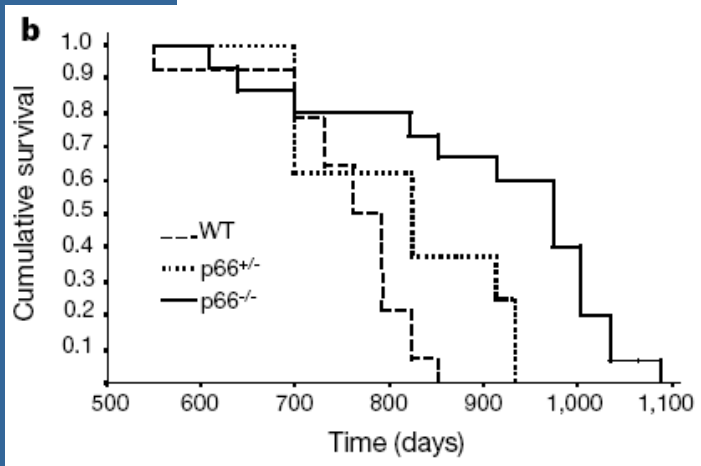
(Liu et al., 2002)

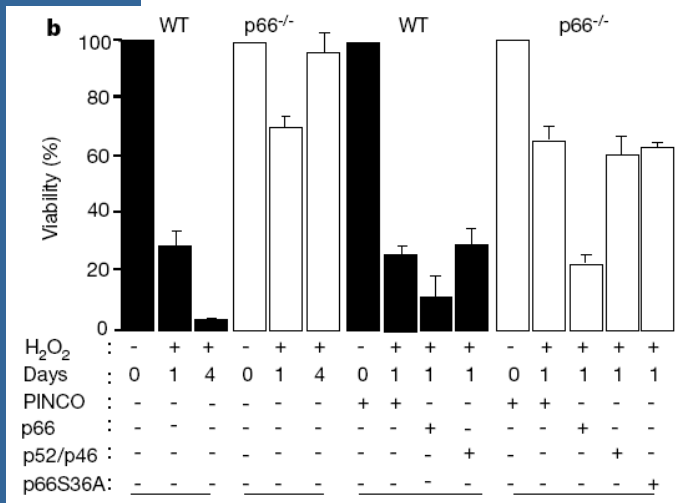
N-acetyl cysteine causes a significant decrease in protein carbonyls, reverses the age-related decline in cytochrome c content and the decrease in cytosolic GSH in the brain (Cocco et al., 2005).

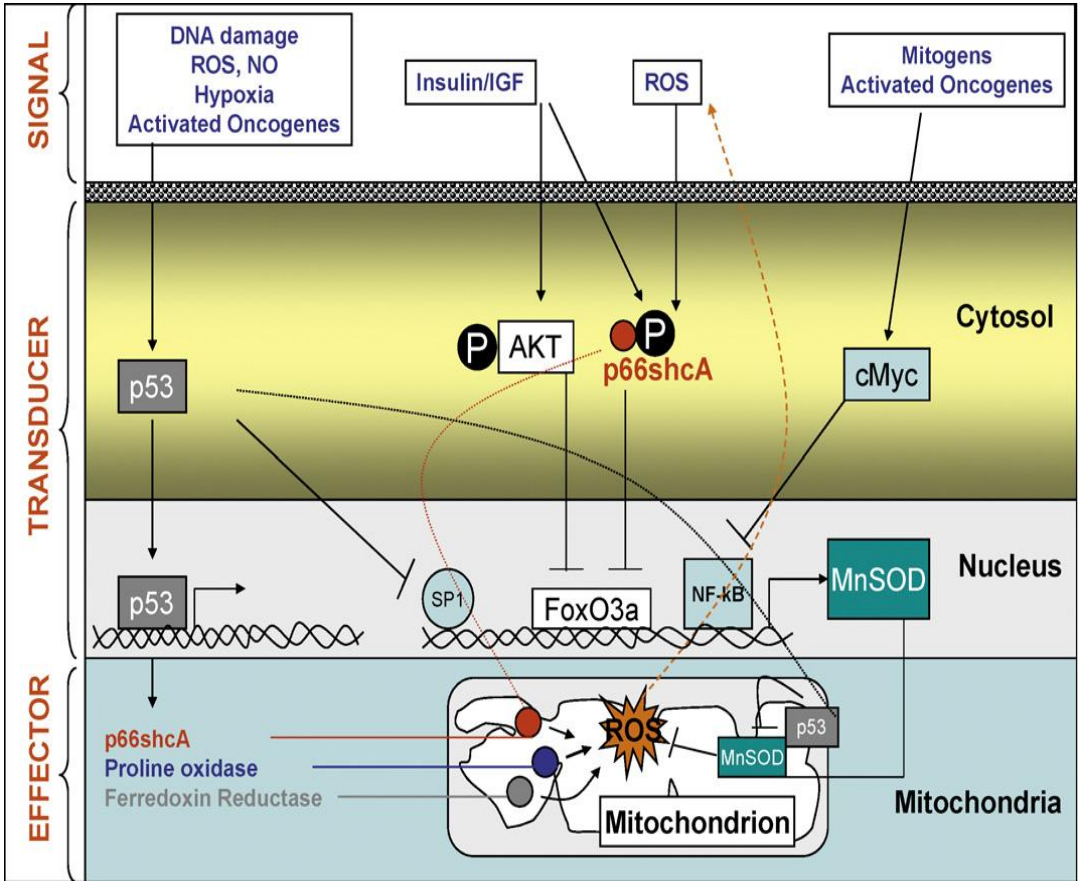
(R)-α-Lipoic acid is a coenzyme involved in mitochondrial redox processes, chelates iron and copper and recycles several antioxidants including GSH and vitamins C and E has been shown to ameliorate memory and brain mitochondrial functions in combination with acetyl-L-carnitine in old rats.

$p66^{shc-/-}$ mice: longer lifespan, higher resistance to oxidative stress and type 2 diabetes

p66Shc, a 66 kDa proto-oncogene Src collagen homologue (Shc) adaptor protein, is classically known as a signalling protein implicated in receptor tyrosine kinase signal transduction.







OPEN ACCESS Freely available online

PLoS one

Nrt1 and Tna1-Independent Export of NAD$^+$ Precursor Vitamins Promotes NAD$^+$ Homeostasis and Allows Engineering of Vitamin Production

Peter Belenky[1], Rebecca Stebbins[1], Katrina L. Bogan[1,2], Charles R. Evans[3], Charles Brenner[1,2]*

1 Departments of Genetics and Biochemistry and Norris Cotton Cancer Center, Dartmouth Medical School, Lebanon, New Hampshire, United States of America, **2** Departments of Biochemistry and Internal Medicine, Carver College of Medicine, University of Iowa, Iowa City, Iowa, United States of America, **3** Molecular Phenotyping Core, University of Michigan Nutrition and Obesity Research Center, Ann Arbor, Michigan, United States of America

Abstract

NAD$^+$ is both a co-enzyme for hydride transfer enzymes and a substrate of sirtuins and other NAD$^+$ consuming enzymes. NAD$^+$ biosynthesis is required for two different regimens that extend lifespan in yeast. NAD$^+$ is synthesized from tryptophan and the three vitamin precursors of NAD$^+$: nicotinic acid, nicotinamide and nicotinamide riboside. Supplementation of yeast cells with NAD$^+$ precursors increases intracellular NAD$^+$ levels and extends replicative lifespan. Here we show that both nicotinamide riboside and nicotinic acid are not only vitamins but are also exported metabolites. We found that the deletion of the nicotinamide riboside transporter, Nrt1, leads to increased export of nicotinamide riboside. This discovery was exploited to engineer a strain to produce high levels of extracellular nicotinamide riboside, which was recovered in purified form. We further demonstrate that extracellular nicotinamide is readily converted to extracellular nicotinic acid in a manner that requires intracellular nicotinamidase activity. Like nicotinamide riboside, export of nicotinic acid is elevated by the deletion of the nicotinic acid transporter, Tna1. The data indicate that NAD$^+$ metabolism has a critical extracellular element in the yeast system and suggest that cells regulate intracellular NAD$^+$ metabolism by balancing import and export of NAD$^+$ precursor vitamins.

Citation: Belenky P, Stebbins R, Bogan KL, Evans CR, Brenner C (2011) Nrt1 and Tna1-Independent Export of NAD$^+$ Precursor Vitamins Promotes NAD$^+$ Homeostasis and Allows Engineering of Vitamin Production. PLoS ONE 6(5): e19710. doi:10.1371/journal.pone.0019710

Editor: Vasu D. Appanna, Laurentian University, Canada

Received February 24, 2011; **Accepted** April 6, 2011; **Published** May 11, 2011

Supplementation of yeast cells with NAD+ precursors (tryptophan, nicotinic acid, nicotinamide) increases intracellular NAD+ levels and extends replicative lifespan.

LONGEVITY MEDICINE REVIEW™
Analyzing the latest research in longevity science

Improvements in Nutrition and Lifestyle Increase Telomerase Activity

by Lara Pizzorno, MDiv, MA, LMT

Can telomerase activity be increased by improvements in diet and lifestyle?

Published in the November 2008 issue of Lancet Oncology, Dr. Dean Ornish's latest research, a pilot study on the effects of dietary and lifestyle changes in 30 men with low risk prostate cancer, suggests the answer is a resounding "Yes!" PBMC telomerase activity in these men increased 29.84% within just 3 months of making significant, yet simple, changes in diet and lifestyle.[1]

Telomerase-Enhancing Diet, Supplement and Lifestyle Program

After a 3-day intensive residential retreat, the men were placed on a low-fat (10% of calories from fat), whole foods, plant-based diet, centered on vegetables, fruits, unrefined grains, and legumes. Intake of refined carbohydrates was minimized. The diet was supplemented with soy (one daily serving of tofu plus 58 grams of a fortified soy protein powdered beverage), fish oil (3 grams daily), vitamin E (100 IU daily), selenium (200 µg daily), and vitamin C (2 grams daily).

In addition, subjects participated in moderate aerobic exercise (walking 30 min/day, 6 days/week); stress management (gentle yoga-based stretching, breathing, meditation, imagery, and progressive relaxation techniques 60 min/day, 6 days/week), and a 1-hour group support session once per week. Participants also met with staff 4 hours per week and had one weekly telephone contact with a study nurse.

Compliance was excellent for both lifestyle and dietary recommendations. After 3 months, subjects reported consuming an average11.6% of calories from fat per day, exercising an average of 3.6 hours each week, and practicing stress management techniques an average of 4.5 hours each week. All medications remained unchanged throughout the 3-month trial, with the exception of participant whose statin drug dosage was decreased.

Telomerase: Anti-Aging Miracle?

The mice involved in the study were given an enzyme called telomerase, 4-OHT, to reactivate the telomeres in the body. The telomeres are found on the ends of chromosomes and serve to protect the chromosome from damage. As aging occurs, the telomeres get smaller and eventually die off.

The mice that showed signs of reversed aging had larger brains after receiving the enzyme. It also reversed loss of fertility. DePinho noted "It gives us a sense that there's a point of return for age-associated disorders," notes *Nature*.

Will telomerase eventually be a drug known to people worldwide? Is this enzyme the magic cure for aging? DePinho was surprised that this enzyme so completely reversed the aging process, rather than just slowing it down, notes the *Daily Mail*.

About TA-65®

TA-65® is a proven telomerase activator* that was discovered by California biotech company Geron, and licensed to T.A Sciences. Our clients take TA-65 capsules in a 12 month program known as the Patton Protocol. TA-65 turns on the hTERT gene* which activates the enzyme telomerase which can lengthen your telomeres. We measure your telomeres before, during and after completing the Protocol to show actual changes in telomere length.

How is TA-65® made?

TA-65 is a naturally occurring single molecule found in the ancient Chinese herb Astragalus. T.A. Sciences has developed a proprietary process to refine and purify TA-65. Our process begins with tons of plant material harvested from selected farms in one small region in China. In our plant extraction facility, the raw Astragalus root is chopped up and refined. After initial extraction, the base ingredient is further purified and then sent to an outside government testing facility where it

J Am Soc Nephrol. 2010 February; 21(2): 327–336. PMCID: PMC2834551
doi: 10.1681/ASN.2009010072.

Telomere Shortening Reduces Regenerative Capacity after Acute Kidney Injury

Jens H. Westhoff,[*] Carolin Schildhorn,[*†] Christoph Jacobi,[†] Meike Hömme,[†] Andrea Hartner,[‡] Heidi Braun,[*] Christine Kryzer,[*] Chunfang Wang,[§] Thomas von Zglinicki,[§] Bettina Kränzlin,[‖] Norbert Gretz,[‖] and Anette Melk[⊠†]

Biochimie. 2008 Jan;90(1):24-32. Epub 2007 Sep 22.

Telomere dysfunction and stem cell ageing.

Ju Z, Lenhard Rudolph K.

Institute of Molecular Medicine and Max-Planck-Research Group on Stem Aging, Ulm University, Ulm, Germany.

Aging Cell. 2011 Apr 25. doi: 10.1111/j.1474-9726.2011.00718.x. [Epub ahead of print]

Comparative Biology of Mammalian Telomeres: Hypotheses on Ancestral States and the Roles of Telomeres in Longevity Determination.

Gomes NM, Ryder OA, Houck ML, Charter SJ, Walker W, Forsyth NR, Austad SN, Venditti C, Pagel M, Shay JW, Wright WE.

Department of Cell Biology. The University of Texas Southwestern Medical Center, Dallas, Texas, 75390-9039, USA. Faculdade de Ciências da Universidade de Lisboa, P-1749-016 Portugal. Conservation and Research for Endangered Species, Genetics Division. Arnold and Mabel Beckman Center for Conservation Research, Escondido, California 92027, USA Keele University Medical School, Stoke on Trent, STA 7QB, UK Barshop Center for Longevity and Aging Studies, San Antonio, Texas 78245, USA. School of Biological Sciences, University of Reading, Reading, Original Paper Berkshire, RG6 6BX, UK Santa Fe Institute, Santa Fe, New Mexico 87501, USA.

Abstract

Progressive telomere shortening from cell division (replicative aging) provides a barrier for human tumor progression. This program is not conserved in laboratory mice, which have longer telomeres and constitutive telomerase. Wild species that do/do not use replicative aging have been reported but the evolution of different phenotypes and a conceptual framework for understanding their uses of telomeres is lacking. We examined telomeres/telomerase in cultured cells from >60 mammalian species to place different uses of telomeres in a broad mammalian context. Phylogeny based statistical analysis reconstructed ancestral states. Our analysis suggested that the ancestral

Display Settings: Abstract

J Orthop Res. 2011 May 16. doi: 10.1002/jor.21451. [Epub ahead of print]

Antitumor effects of telomerase inhibitor TMPyP4 in osteosarcoma cell lines.

Fujimori J, Matsuo T, Shimose S, Kubo T, Ishikawa M, Yasunaga Y, Ochi M.

Department of Orthopaedic Surgery, Graduate School of Biomedical Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-k

Pflugers Arch. 2011 Mar 29. [Epub ahead of print]

Klotho: a novel regulator of calcium and phosphorus homeostasis.

Huang CL, Moe OW.

Department of Internal Medicine, Charles and Jane Pak Center of Mineral Metabolism and Clinical Research, University of Texas Southwestern Medical Center, Dallas, TX, 75390-8856, USA, chou-long.huang@utsouthwestern.edu.

Abstract

Klotho which was originally identified as an anti-aging protein is emerging as a substance with multiple effects on many systems including mineral homeostasis. In addition to

Am J Kidney Dis. 2011 Apr 14. [Epub ahead of print]

Role of Klotho in Aging, Phosphate Metabolism, and CKD.

John GB, Cheng CY, Kuro-O M.

Department of Pathology, University of Texas Southwestern Medical Center at Dallas, Dallas, TX.

Abstract

The klotho gene (KL) was identified first as a putative aging-suppressor gene that extended life span when overexpressed and accelerated aging-like phenotypes when disrupted in mice. It encodes a single-pass transmembrane protein and is expressed predominantly in kidney, where it functions as an obligate coreceptor for fibroblast growth factor 23 (FGF-23). FGF-23 is a bone-derived hormone that suppresses phosphate reabsorption and 1,25 dihydroxyvitamin D(3) (vitamin D) synthesis in the kidney. Klotho also is expressed in the parathyroid gland, where FGF-23 decreases parathyroid hormone expression and secretion, further suppressing vitamin D synthesis in kidney. Thus, FGF-23 functions as a phosphaturic hormone and a counter-regulatory hormone for vitamin D, thereby inducing negative phosphate balance. Mice lacking either FGF-23 or Klotho show hyperphosphatemia in addition to developing multiple aging-like phenotypes, which can be rescued by resolving phosphate retention. These findings have

Nephrol Dial Transplant. 2011 May 12. [Epub ahead of print]

Lack of association of Klotho gene variants with valvular and vascular calcification in Caucasians: a candidate gene study of the Framingham Offspring Cohort.

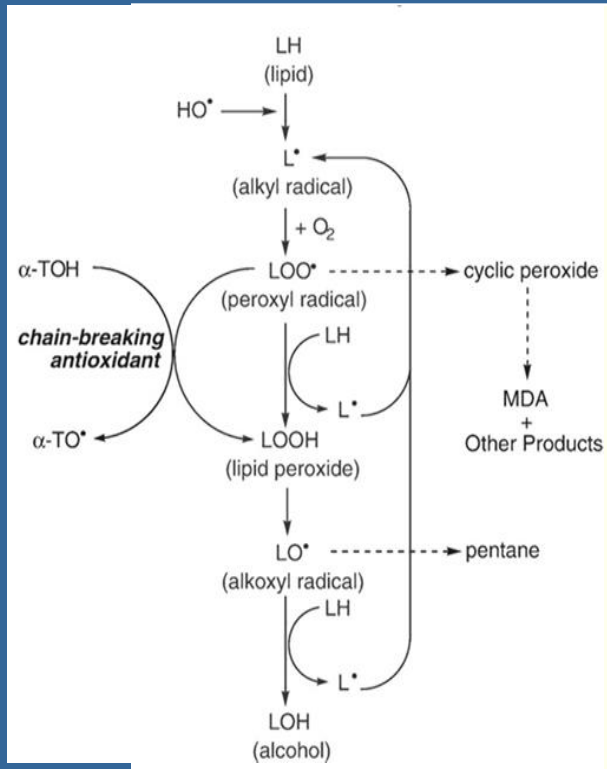
Tanqri N, Alam A, Wooten EC, Huggins GS.

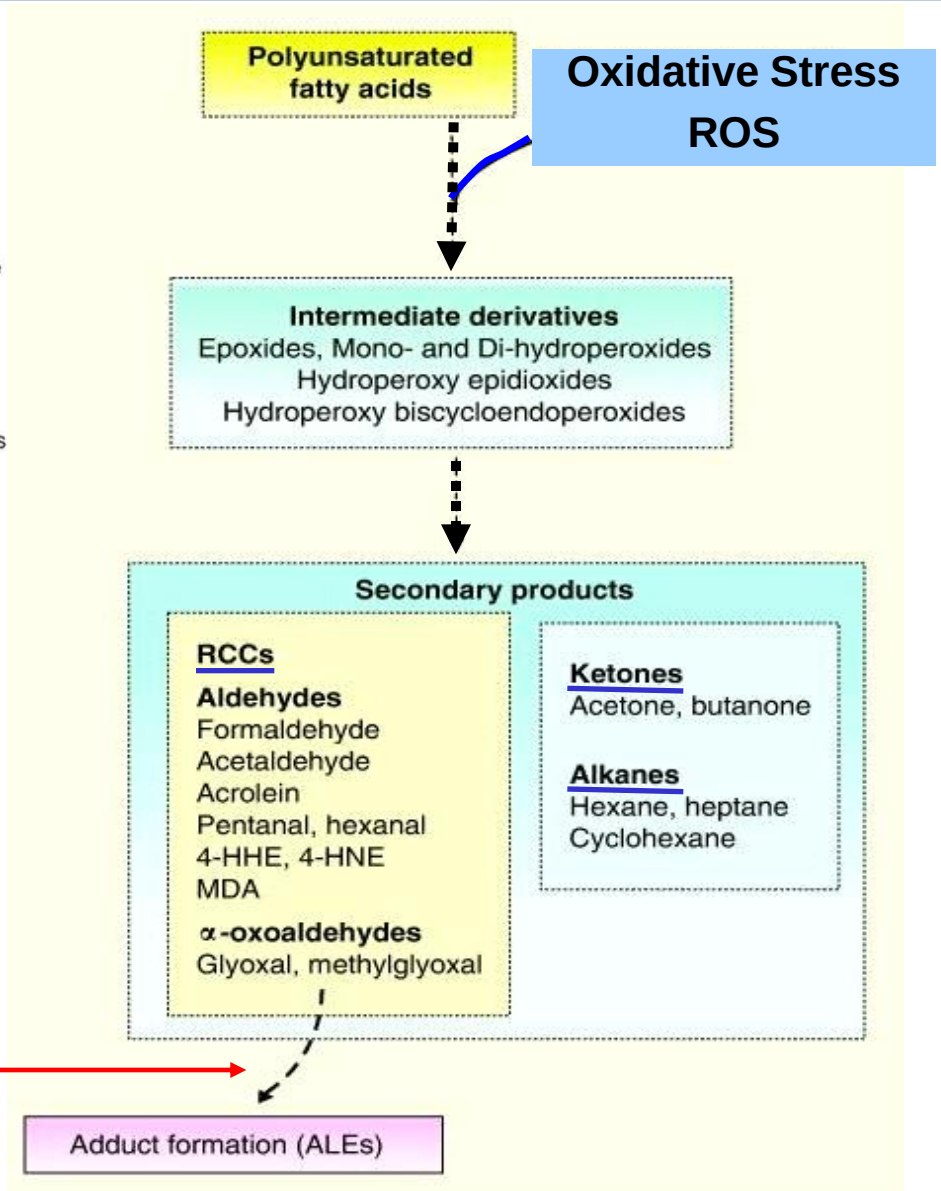
1Division of Nephrology, Department of Medicine, Tufts Medical Center, Boston, USA.

Abstract

BACKGROUND: Valvular and vascular calcification are important early aging phenotypes and represent risk factors for cardiovascular morbidity and mortality. Klotho is a gene primarily expressed in the kidney that has an important role in calcium-phosphate homeostasis. The functional KL-VS variant of Klotho has been associated with aging and cardiovascular disease in human studies, but its role in valvular and vascular calcification remains unknown. We performed a candidate gene study in the Framingham Offspring Cohort to evaluate the effect of KL-VS variant of the Klotho gene on valvular calcification.

Formation of ALEs and ALE precursors

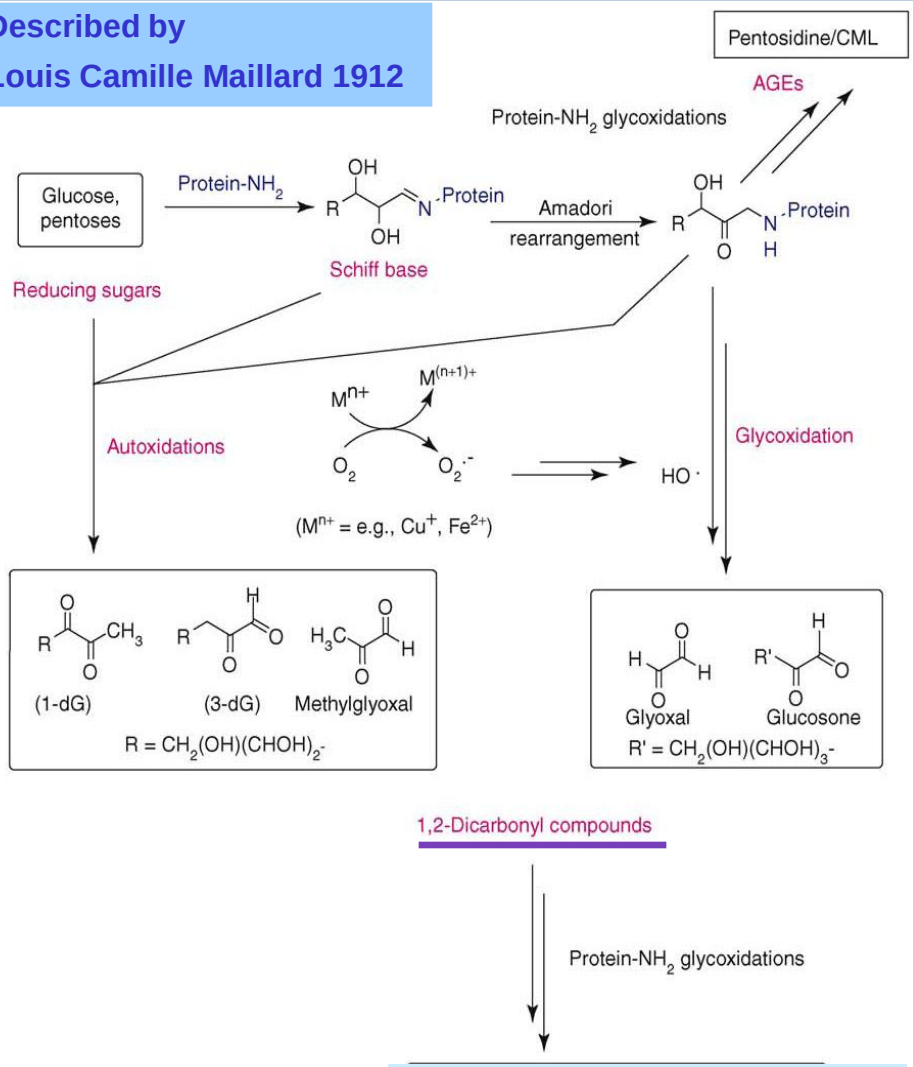




Negre-Salvayre A (2008) Brit. J Pharmacol 153: 6–20

Formation of Reactive carbonyl compounds and AGEs

Described by
Louis Camille Maillard 1912

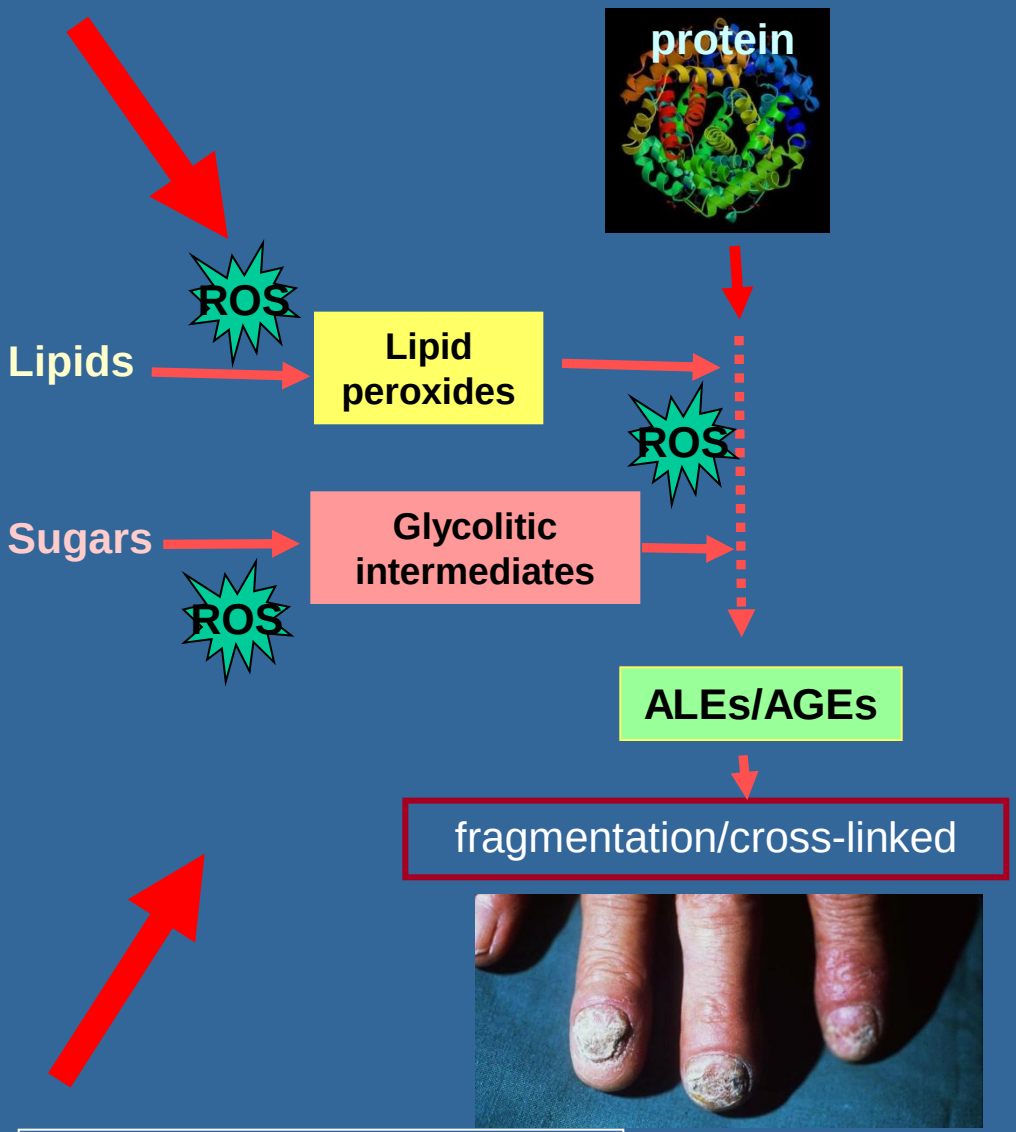


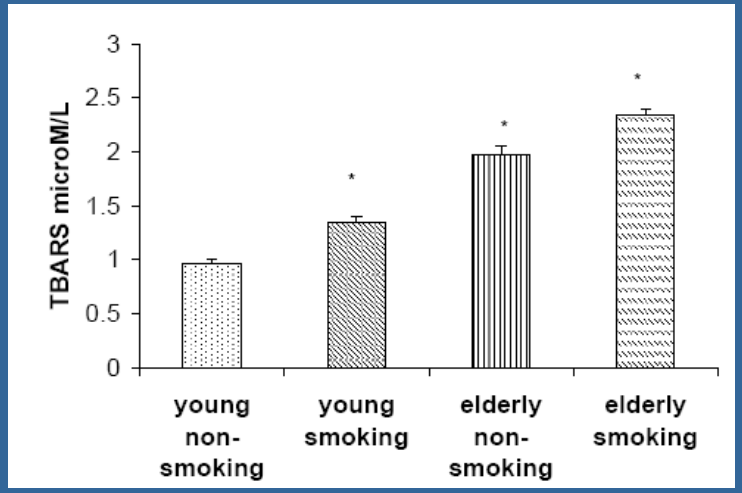
AGEs **Pentozidine, Argpyrimidine Pyyraline, Glucosepane Hydroimidazolone, CML**

RCCs (α-oxoaldehydes) are basically generates during diabetes and hyperglycaemia, from the Maillard reaction, which involves the condensation of sugars with proteins, leading to the formation of a Schiff bases, followed by a rearrangement (non-enzymatic glycosylation: glycation) generating the comparatively stable Amadori product. Further degradation, like deamination and hydrolyzation, of this product can create secondary products, various unsaturated carbonyls, e.g. a-oxoaldehydes (methylglyoxal and glyoxal)

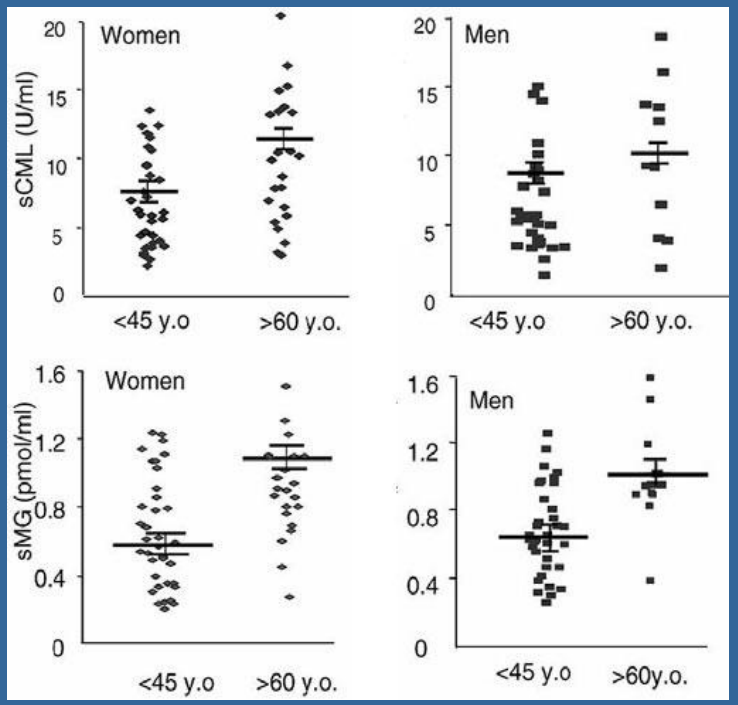
Thornalley et al., 199.; Baynes, 2000

Free radical theory of aging





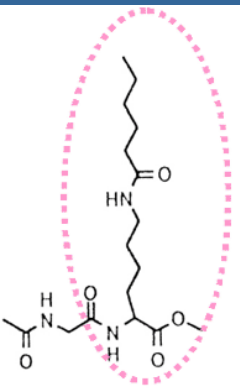
Garoka & Skibska,2006 **Carboxymethyl lysine**



Peppa et al., 2008 **Methylglyoxal**

Glycation theory of aging

Oxidative modification of proteins with lipid peroxidation by-products



Structure of HEL
N ε -(Hexanoyl) Lysine: HEL

Lipid peroxide modified proteins

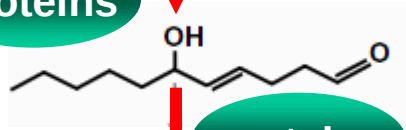
n-6 PUFAs
(linoleic and arachidonic acids)

ROS
"peroxidation"

n-3 PUFAs
(docosahexaenoic, eicosapentaenoic and linolenic acid)

Hydroperoxides

proteins



4-HNE

proteins

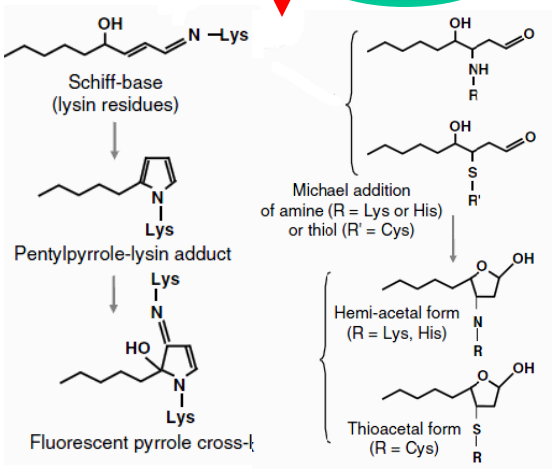
4-HHE

MDA

Acrolein

proteins

Aldehyde modified proteins



Aldehyde modified proteins

The modification and cross-linking

Losing of molecular fidelity
altering progressively the structure and function of the proteins

Signalling properties of ALEs and ALE precursors

Petersen and Doorn, 2004

LDL

ROS

LDL oxidation

protein

oxidized phospholipids (OxPLs),

4-HNE

oxidized cholesterol derivatives (oxysterols)

Endogenous sources

1) Non enzymatic pathways
2) Enzymatic pathways

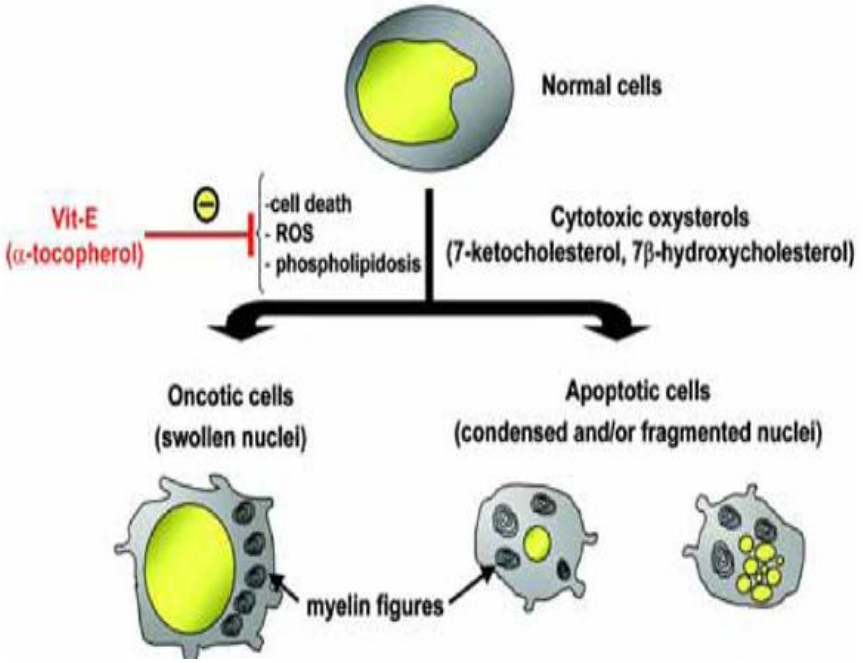
ATHEROSCLEROSIS

ORIGIN OF PLASMA AND TISSUE OXYSTEROLS

Exogenous source

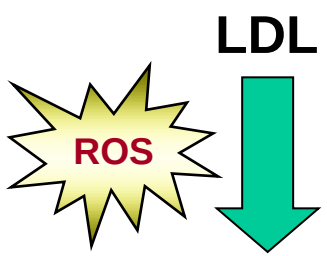
Mainly formed by autoxidation of foodstuff

(induced by heat, light exposure, refrigeration, freeze-drying)



ORIGIN OF PLASMA AND TISSUE OXYSTEROLS

Petersen and Doorn, 2004



LDL

LDL oxidation

protein

oxidized phospholipids (OxPLs),

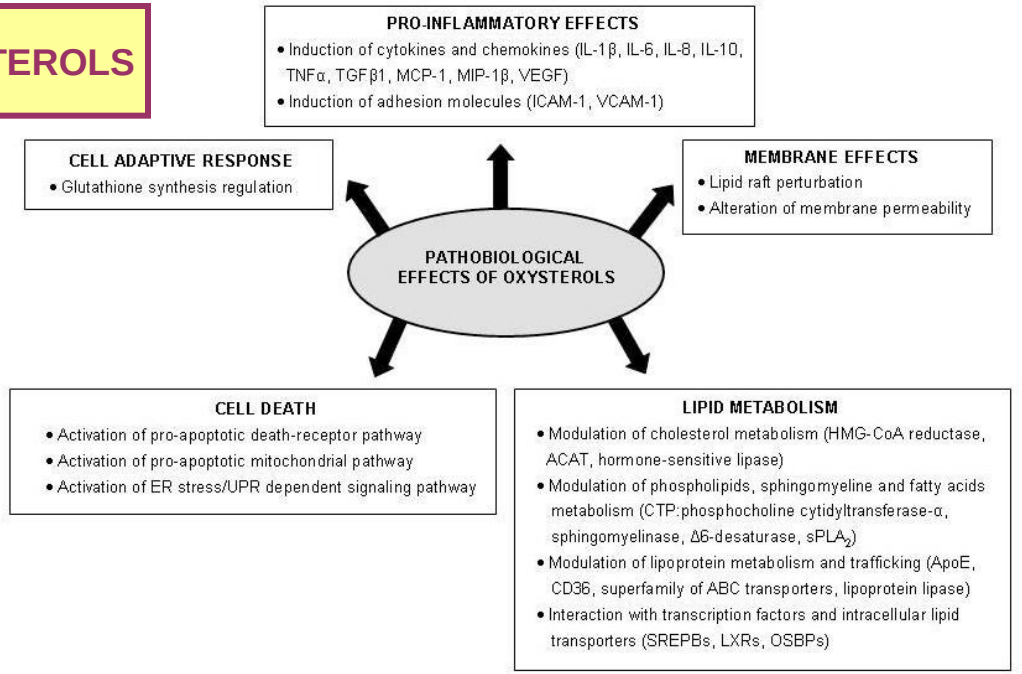
4-HNE

oxidized cholesterol derivatives (oxysterols)

Endogenous sources

1) Non enzymatic pathways
2) Enzymatic pathways

ATHEROSCLEROSIS

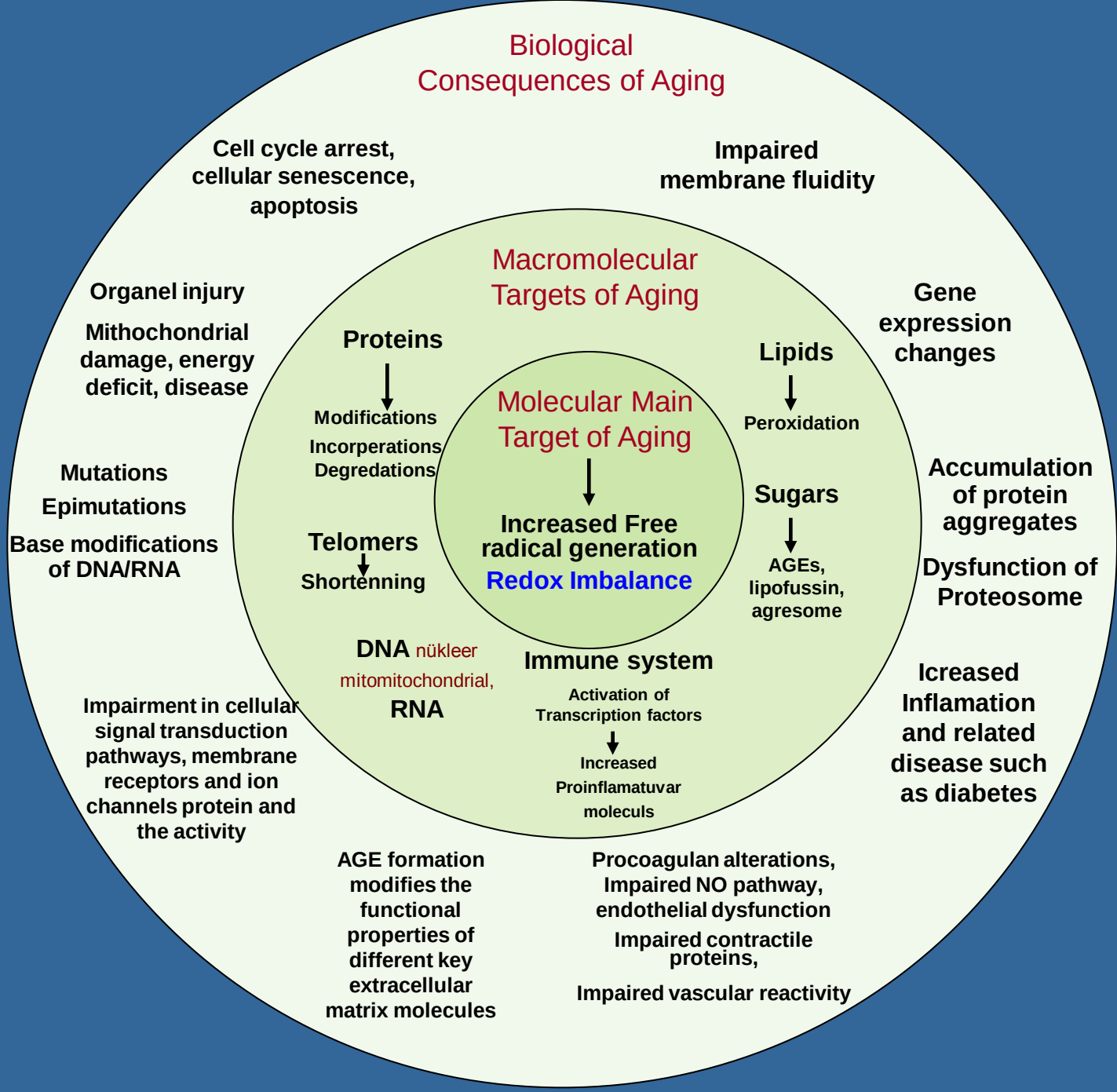


FLAVONLAR

POLIFENOLLER

THE REALITY

End products of oxidative modifications of lipids and proteins are accumulated in tissues by age



Oxidized Protein Accumulation in Ageing

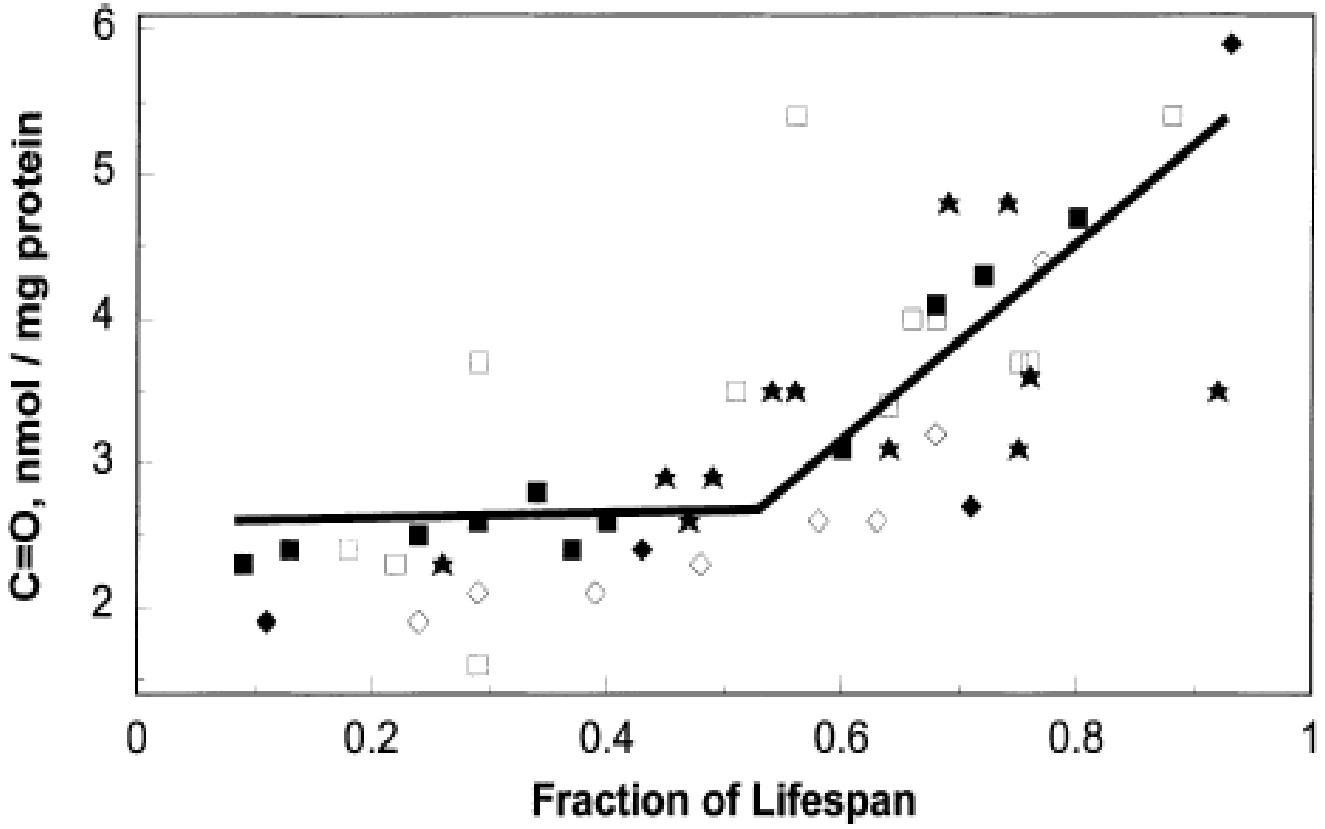


Fig. 1. Carbonyl content of protein from different tissues. One observes a dramatic increase in oxidized protein during the last third of the lifespan. The line is the semi-logarithmic fit to all the data points. The data points were taken from published reports: ■, human dermal fibroblasts in tissue culture (Oliver et al., 1987); ★, human lens (Garland, 1990); □, human brain obtained at autopsy (Smith et al., 1991); ◆, rat liver (Starke-Reed and Oliver, 1989); and ◇, whole fly (Sohal et al., 1993).

Shanmugam et al., 2008

AGE/ALE levels increase during aging and in diseases like diabetes

The capacity of the proteasomal system as well as of lysosomal proteases decreases during aging

(Chowdhury et al., 2004

OXIDATIVELY DAMAGED PROTEIN

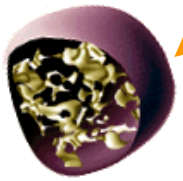
(2) Increasingly oxidized & disfolded Protein

PROTEOLYSIS

proteasomal system

OXIDATIVE STRESS

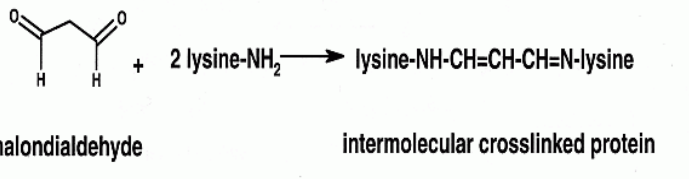
(3) Severely oxidized & covalent cross-linked Protein



lysosomal system

HNE-Protein Adducts inhibits proteasome activity

MDA-adducts



Aggregates Accumulation

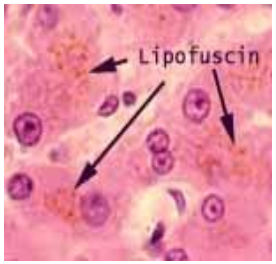
oxidatively modified cellular organelles

DEGRADATION

Peptides & Amino acids

AGEING

LIPOFUSCIN



Lipofuscin

A highly cross-linked cellular protein, reduces proteosomal and lysosomal degradation capacity

Lipofuscin accumulation in Aging

Beal, 2004

Jung et al., 2007

Lukiw & Bazan, 2008

in retina

age-dependent macular degeneration & retinal pigment epithelium ages

tyrosine dihydroxyphenylalanine

Ox. Stress

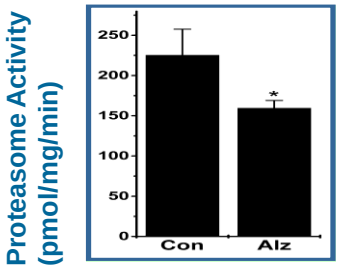
melanin

protein

Protein-melanin adducts

Melanosomes degredation

β-amyloid deposition Mitochondrial dysfunction



Neurodegenerative disorders

Alzheimer's-Parkinson

hippocampal CA3 pyramidal neurons

impaired memory acquisition

Chronic green tea consumption prevents age-related changes in hippocampal lipofuscin accumulation.

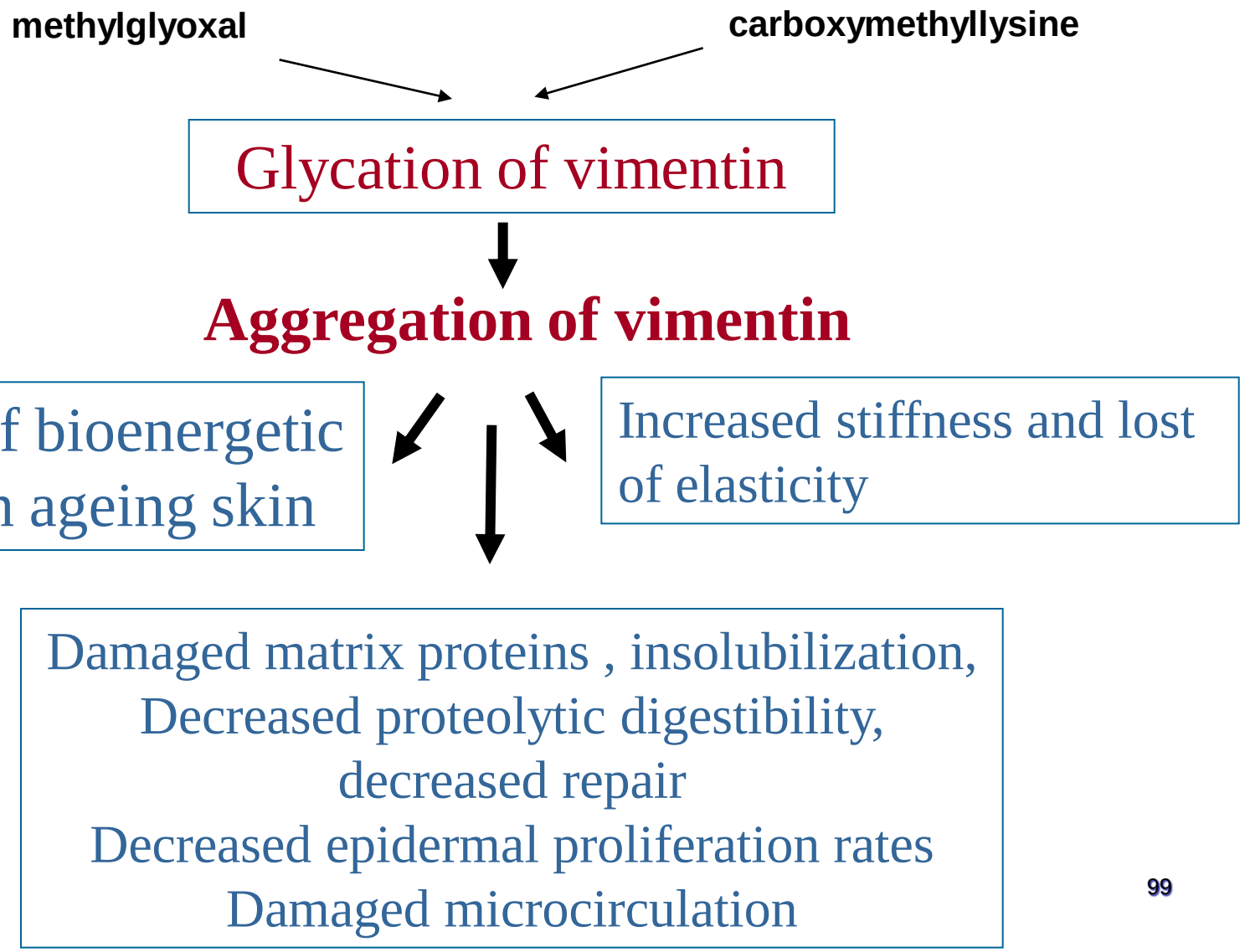
Assunção et al., 2009

Lipoic Acid

Coenzyme Q10

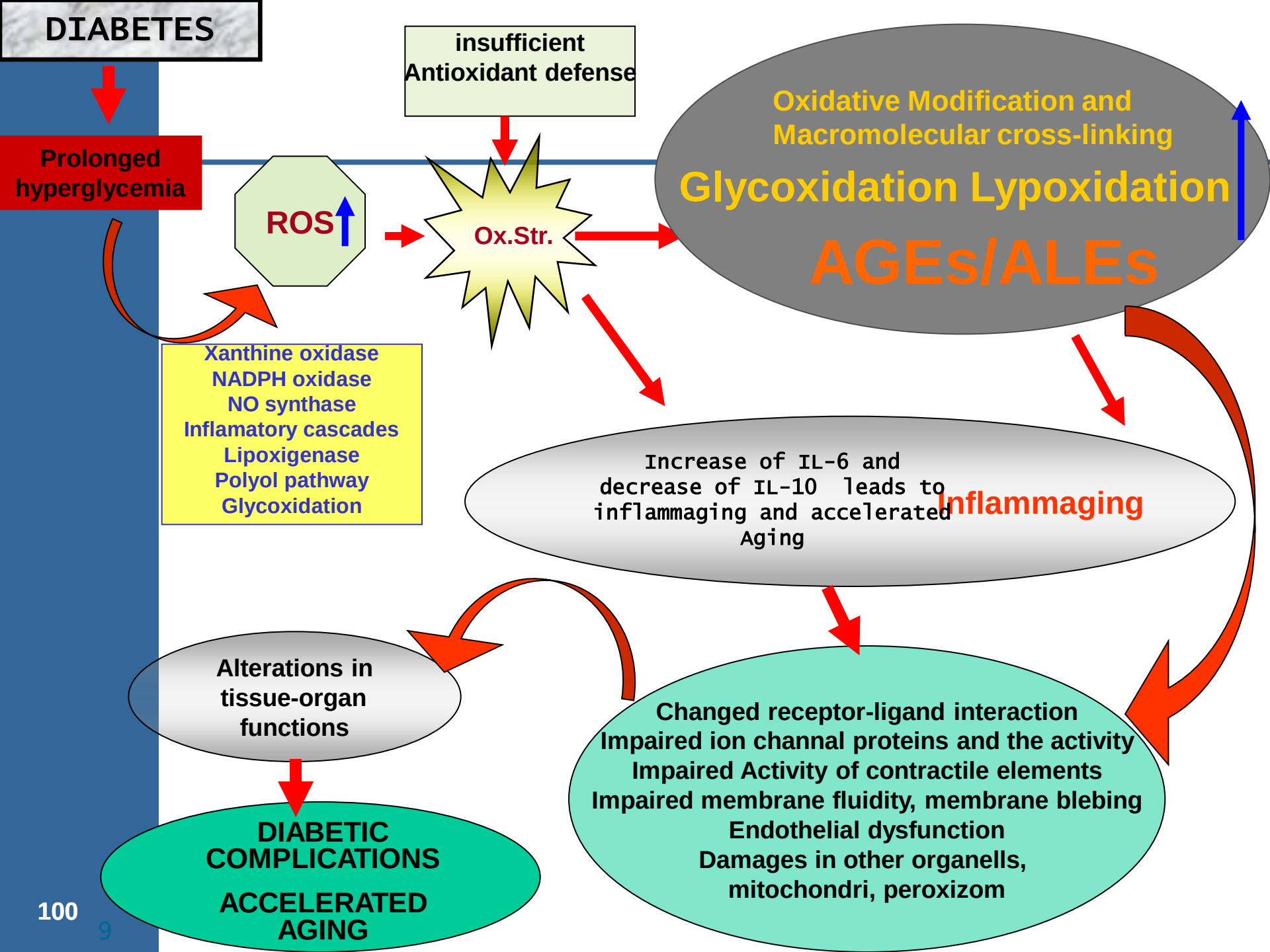
DHA

Glycation and Skin Aging

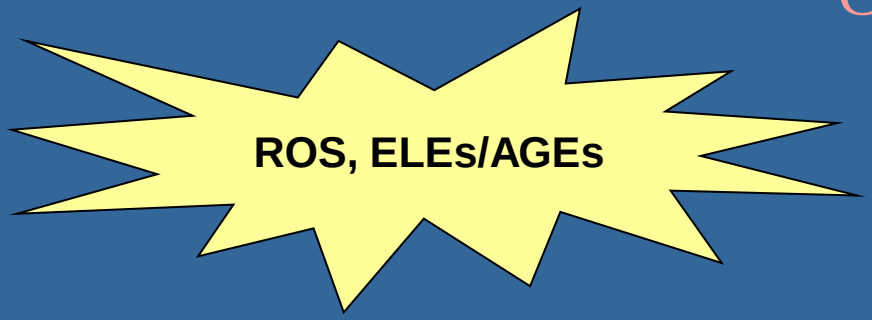


Kueper et al., 2008

99


DIABETES
insufficient
Antioxidant defense
Prolonged
hyperglycemia
ROS
Ox.Str.
Oxidative Modification and
Macromolecular cross-linking
Glycoxidation Lypoxidation
AGEs/ALEs
Xanthine oxidase
NADPH oxidase
NO synthase
Inflamatory cascades
Lipoxigenase
Polyol pathway
Glycoxidation
Increase of IL-6 and
decrease of IL-10 leads to
inflammaging and accelerated
Aging
Inflammaging
Alterations in
tissue-organ
functions
Changed receptor-ligand interaction
Impaired ion channal proteins and the activity
Impaired Activity of contractile elements
Impaired membrane fluidity, membrane blebing
Endothelial dysfunction
Damages in other organells,
mitochondri, peroxizom
DIABETIC
COMPLICATIONS
ACCELERATED
AGING

AGEs/ALEs have been implicated in age-related disease and aging itself, convincingly enough that significant effort has gone into finding **compounds** that can **"prevent","break"** and/or **"reverse"** them.



Vessels
Atherosclerosis

Diabetes, complications

Skin Disorders
Age pigment

Cardiomyopathy
Heart attack

Gastro intestinal
Hepatitis

Eye
Cataractogenesis
Rethinoparhy

Joints
Arthritis

Multiorgan failure
Cancer

Brain
Stroke
Alzheimer

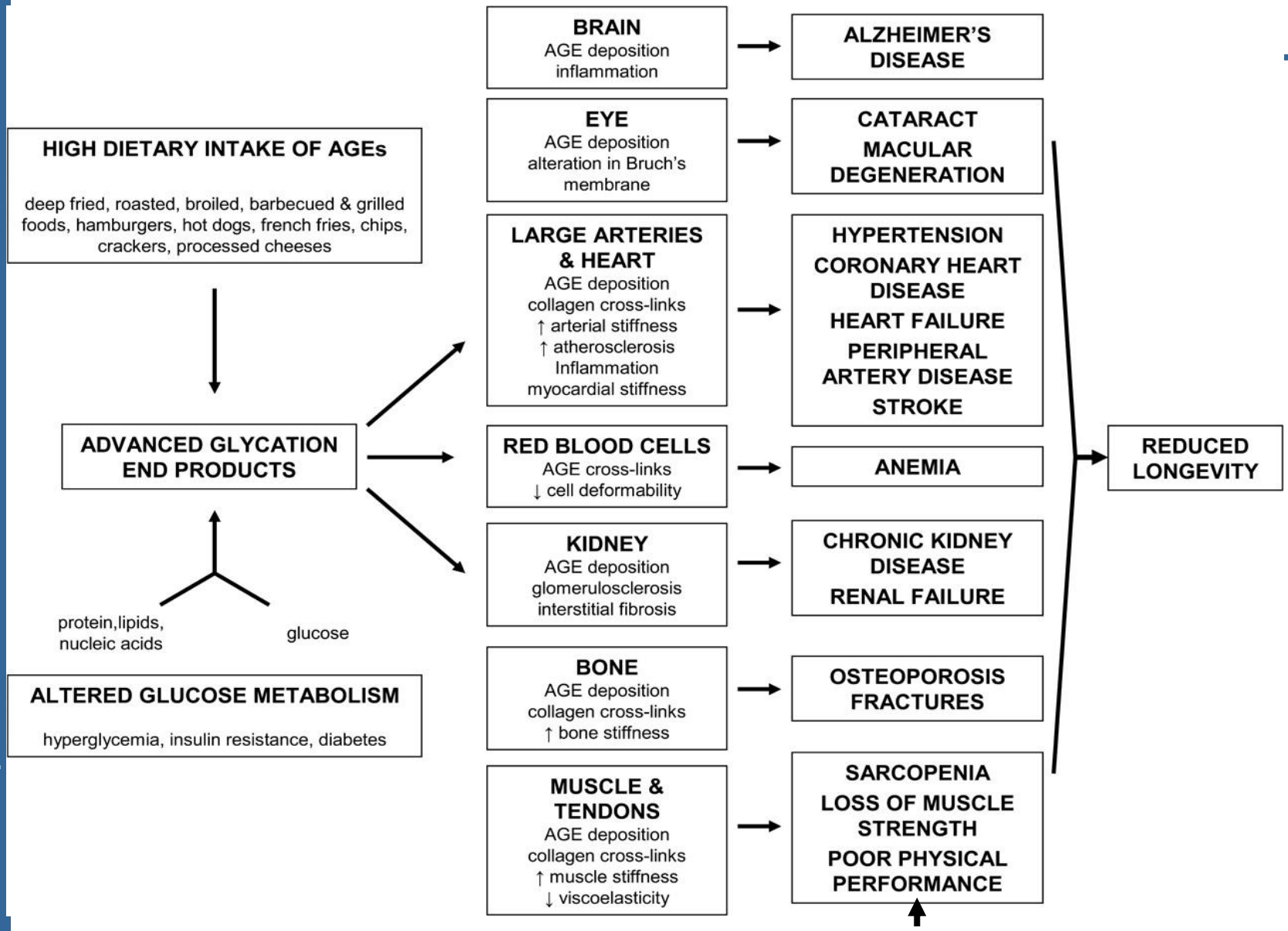
Lung
Asthma

Teeth
Periodontis

Med Res Rev. 2008 Jul;28(4):569-631

Free Radical Biology & Medicine, Vol. 37, No. 11, pp. 1694–1702, 2004

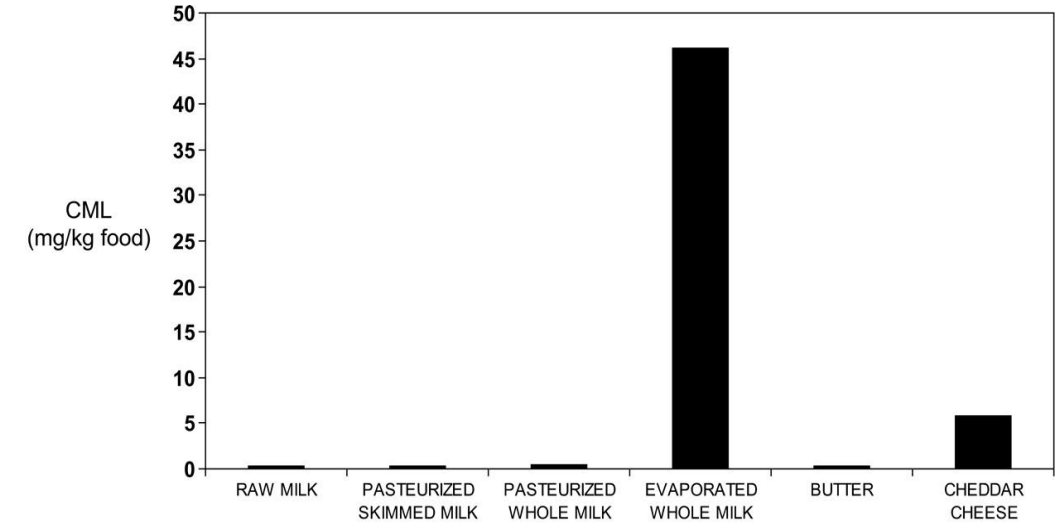
Conceptual model of the effects of AGEs in multiple organ systems during aging.

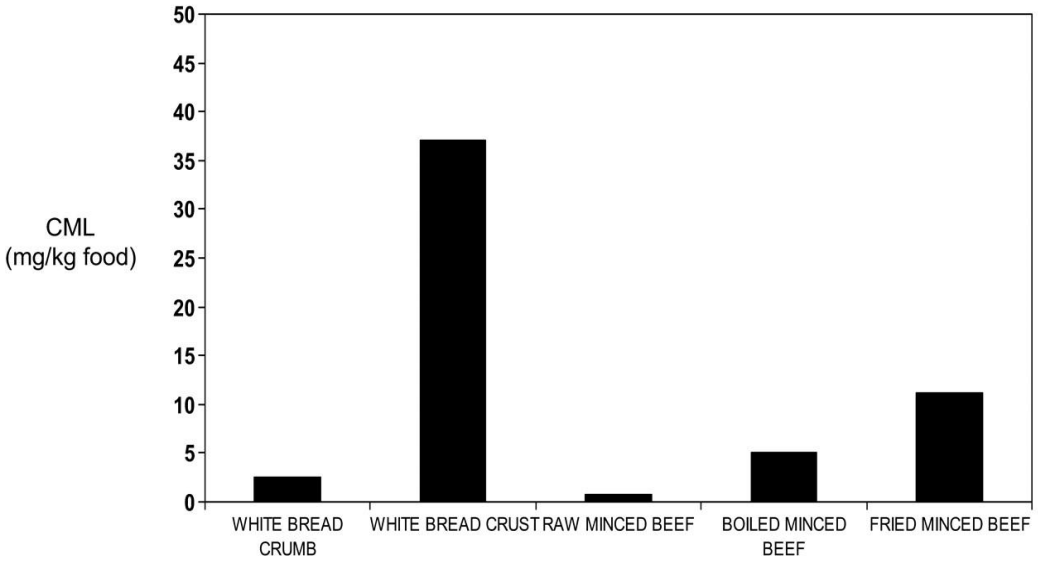


Negative Aspects of AGEs

Semba R D et al. J Gerontol A Biol Sci Med Sci 65A:963-975, 2010

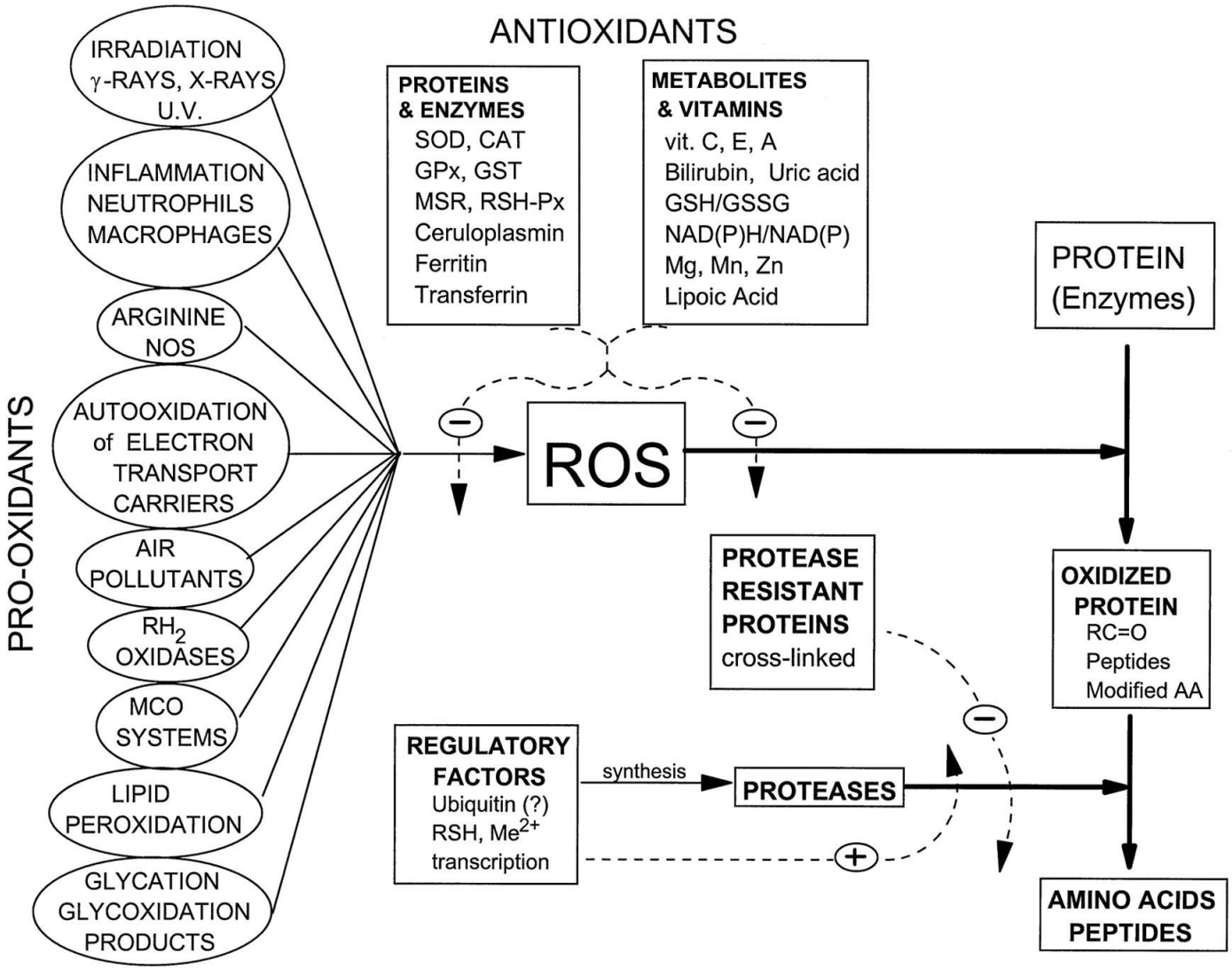
Carboxymethyl-lysine content of selected dairy products, bread, and meat using liquid chromatography–mass spectrometry.





Semba R D et al. J Gerontol A Biol Sci Med Sci 2010;65A:963-975

Accumulation of oxidized protein is dependent on the balance between pro-oxidant, antioxidant, and proteolytic activities



Çatalgöl & Grune, 2009

Berlett & Stadtman Biol. Chem. 1997;272:20313-20316

Journal of Gerontology: MEDICAL SCIENCES
Cite journal as: J Gerontol A Biol Sci Med Sci. 2010 September;65A(9):963–975
doi:10.1093/gerona/glq074

Advance Access published on May 17, 2010

GSA65
GETTING BETTER WITH AGE

Does Accumulation of Advanced Glycation End Products Contribute to the Aging Phenotype?

Richard D. Semba,[1] Emily J. Nicklett,[2] and Luigi Ferrucci[3]

YES: Because the accumulation of AGEs accelerate the multisystem functional decline that occurs with aging, and therefore contribute to the aging phenotype.

Exposure to AGEs can be effectively reduced by restriction of dietary intake of AGEs .

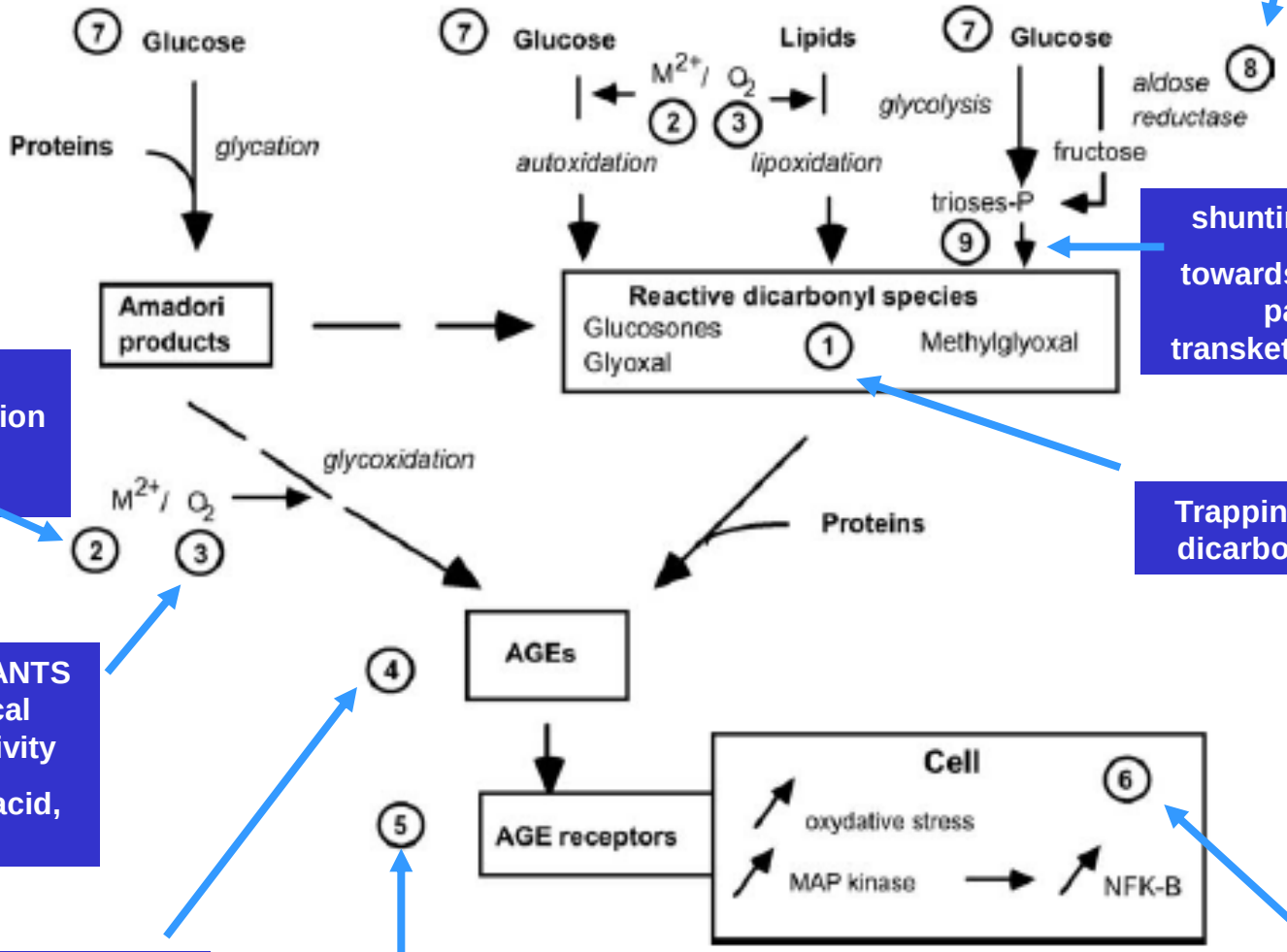
Modification of intake and circulating levels of AGEs is an important strategy to promote health in old age, especially because most Western foods are processed at high temperature and are rich in AGEs.

glycemia reduction by anti-diabetic therapy

metformin

aldose reductase inhibition

Sorbinil, epalrestat



shunting of trioses-P towards the pentose-P pathway by transketolase activation

ANTIOXIDANT activity by transition metal (M2+) chelation

Trapping of reactive dicarbonyl species:

other ANTIOXIDANTS with free radical scavenging activity

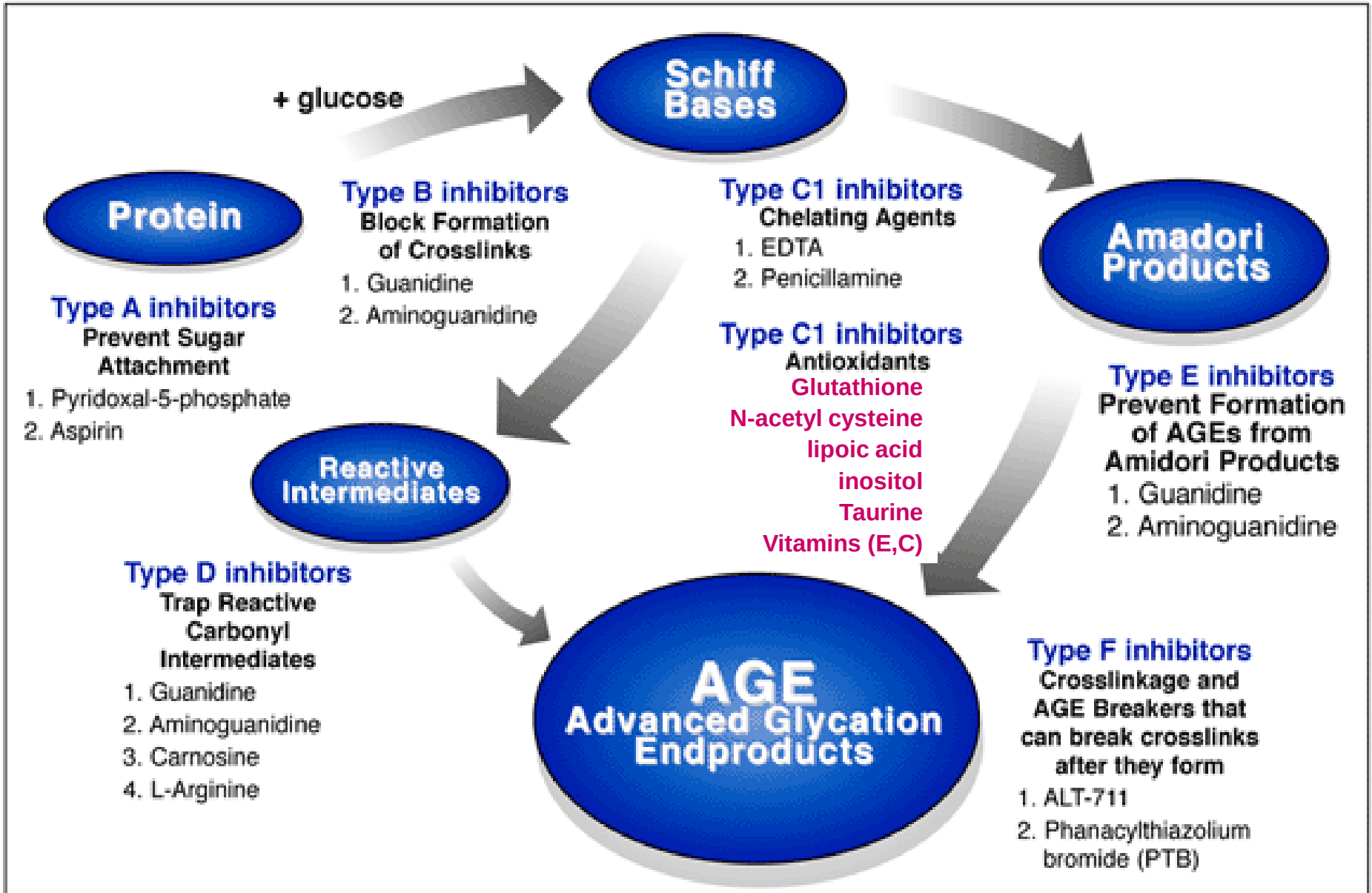
Vit E, Ascorbic acid, Flavonoids

AGE cross-link cleavage (by AGE breakers)

AGE receptor (RAGE) blocking

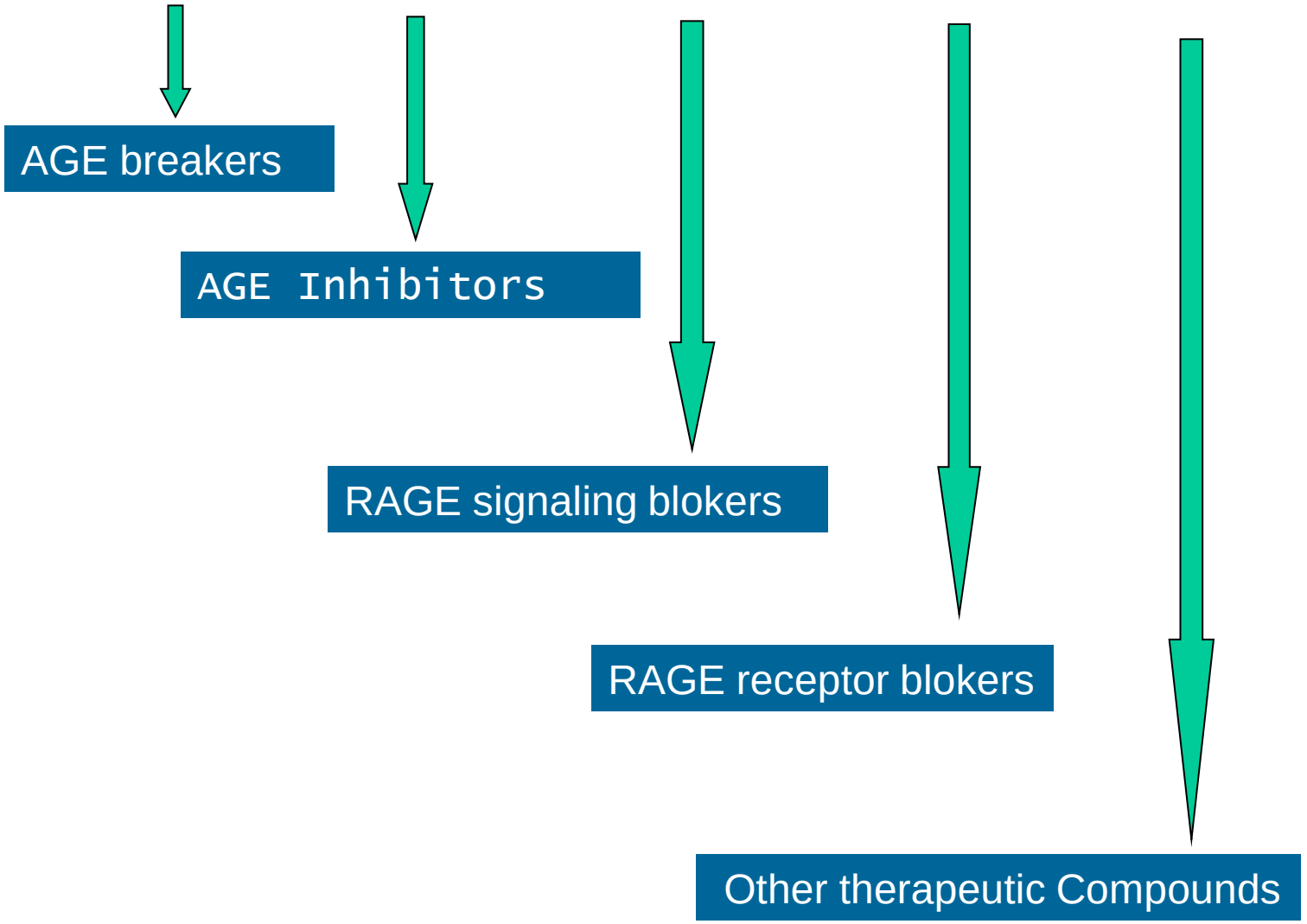
AGE receptor (RAGE) signaling blocking

Cerivastatin, Curcumin



Pridoxin
Pridoxamine

Pharmacological inhibitors of AGEs/ALEs



Peyroux & Sternberg, Pathologie Biologie, 54:405-419, 2006

Horm Metab Res. 2011 Sep;43(10):687-92. Epub 2011 Sep 19.

Lonidamine Extends Lifespan of Adult Caenorhabditis elegans by Increasing the Formation of Mitochondrial Reactive Oxygen Species.

Schmeisser S, Zarse K, Ristow M.

Department of Human Nutrition.

Glycolytic Inhibitor: Lonidamine

Abstract

Compounds that delay aging in model organisms may be of significant interest to antiaging medicine, since these substances potentially provide pharmaceutical approaches to promote healthy lifespan in humans. The aim of the study was to test whether pharmaceutical concentrations of the glycolytic inhibitor lonidamine are capable of extending lifespan in a nematodal model organism for aging processes, the roundworm Caenorhabditis elegans. Several hundreds of adult C. elegan were maintained on agar plates and fed E. coli strain OP50 bacteria. Lonidamine was applied to test whether it may promote longevity by quantifying surv and absence of the compound. In addition, several biochemical and metabolic assays were performed with nematodes exposed to lonidamine. Lonidamine significantly extends both median and maximum lifespan of C. elegans when applied at a concentration of 5 micromolar by 8% each. Moreover, the compound increases paraquat stress resistance, and promotes mitochondrial respiration, culminating in increased formation of reactive oxygen species (ROS). Extension of lifespan requires activation of pmk-1, an orthologue of p38 MAP kinase, and is abolished by co-application of an antioxidant, indicating that increased ROS formation is required for the extension of lifespan by lonidamine. Consistent with the concept of mitohormesis, lonidamine is capable of promoting longevity in a pmk-1 sensitive manner by increasing formation of ROS.

Rejuvenation Res. 2011 Aug;14(4):437-41.

Rapamycin as an antiaging therapeutic?: targeting Mammalian target of rapamycin to treat hutchinson-gilford progeria and neurodegenerative diseases.

Mendelsohn AR, Larrick JW.

Panorama Research Institute and Regenerative Sciences Institute , Sunnyvale, California.

mTORC1 signalling inhibitor: Rapamycin

Abstract

Abstract Mammalian target of rapamycin (mTOR), a serine/threonine kinase and component of the mTORC1 signaling complex, acts as an energy, nutrient, growth factor, stress, and redox sensor to increase protein synthesis and decrease macroautophagy. mTORC1 plays a central role in the maintenance of homeostasis and its deterioration, seen in aging. The Food and Drug Administration (FDA)-approved immunosuppressive macrolide rapamycin binds immunophilin FKBP12 (FK506-binding protein) to inhibit mTORC1. Unlike most other interventions tested to date, inhibition of mTORC1 by rapamycin extends life span in old mice, likely by a combination of increased autophagy and decreased mRNA translation. Hutchinson-Gilford progeria syndrome (HGPS) is a lethal genetic disorder affecting children that is characterized by symptoms of premature aging, such as atherosclerosis. Increased autophagy induced by rapamycin reduces accumulation of progerin, an alternate spliced form of lamin A/C, that forms insoluble toxic aggregates, resulting in reduced HGPS-associated nuclear blebbing, growth inhibition, epigenetic dysregulation, and genomic instability. Rapamycin-induced autophagy also suppresses symptoms in mouse models of Alzheimer, Parkinson, and Huntington diseases, where toxic insoluble protein aggregates accumulate. On the basis of these results, modulation of mTORC1 function is a promising target for the development of therapeutics for neurodegenerative diseases and HGPS. Rapamycin is the obvious candidate for near-term evaluation in the treatment of these diseases. However, the substantial set of rapamycin-associated adverse effects, as well as the lack of aging-specific human data, should caution the routine use of rapamycin as an antiaging agent. The use of safer, but perhaps weaker, indirect mTORC1 inhibitors, such as metformin and resveratrol, may prove useful. Further study will ascertain whether such compounds extend human health or life span.

Pyridoindole antioxidants inhibits AGES/ALEs production in vitro and in vivo

Glucose + Protein → Schiff Base → Amadori Product

Protein carbonylation

Stobadine

AGEs

ALEs

Stobadine inhibits formation of AGEs and ALEs by interfering with processes of advanced glycosylation and lypoxidation.

Lipids + ROS → Lipid hydroperoxides

Stobadine

Rackova et al., 2006

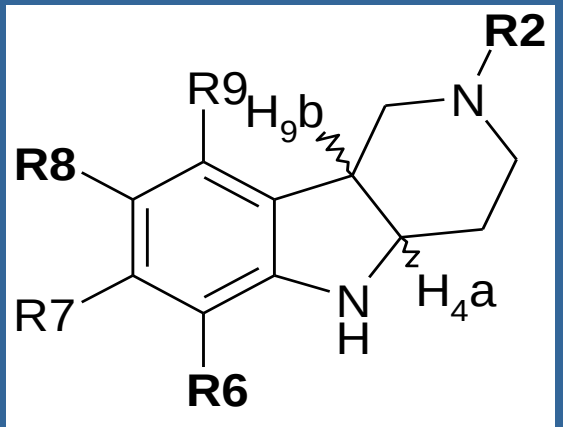
Cumaoglu et al., 2007, 2010

Stefek et al., 2008

Karasu, 2010 review

substituted hexahydropyridoindoles

POVERFULL ANTIOXIDANT



In vivo treatment with stobadine prevents lipid peroxidation, protein glycation and calcium overload but does not ameliorate Ca^{2+}-ATPase activity in heart and liver of streptozotocin-diabetic rats: comparison with vitamin E

The ADIC (Antioxidants in Diabetes-Induced Complications) Study Group, Bilgehan Pekiner[a], Das-Evcimen[a], Meral Sahilli[c], Fugen Aktan[a], Milan Stefek[d], Svorad Stolc[d] and Çimen Karasu

Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease Volume 1588, Issue 1, 9 October 2002, Pages 71-78

Methods Find Exp Clin Pharmacol 2002, 24(9): 565
ISSN 0379-0355

CCC: 0379-0355

The pyridoindole antioxidant stobadine attenuates albuminuria, enzymuria, kidney lipid peroxidation and matrix collagen cross-linking in streptozotocin-induced diabetic rats

Stefek, M., Gajdosik, A., Tribulova, N., Navarova, J., Volkovova, K., Weismann, P., Gajdosikova, A., Drimal, J., Mihalova,

Molecular Vision 2005; 11:56-65 <http://www.molvis.org/molvis/v11/a6>
Received 18 August 2004 | Accepted 18 January 2005 | Published 19 January 2005

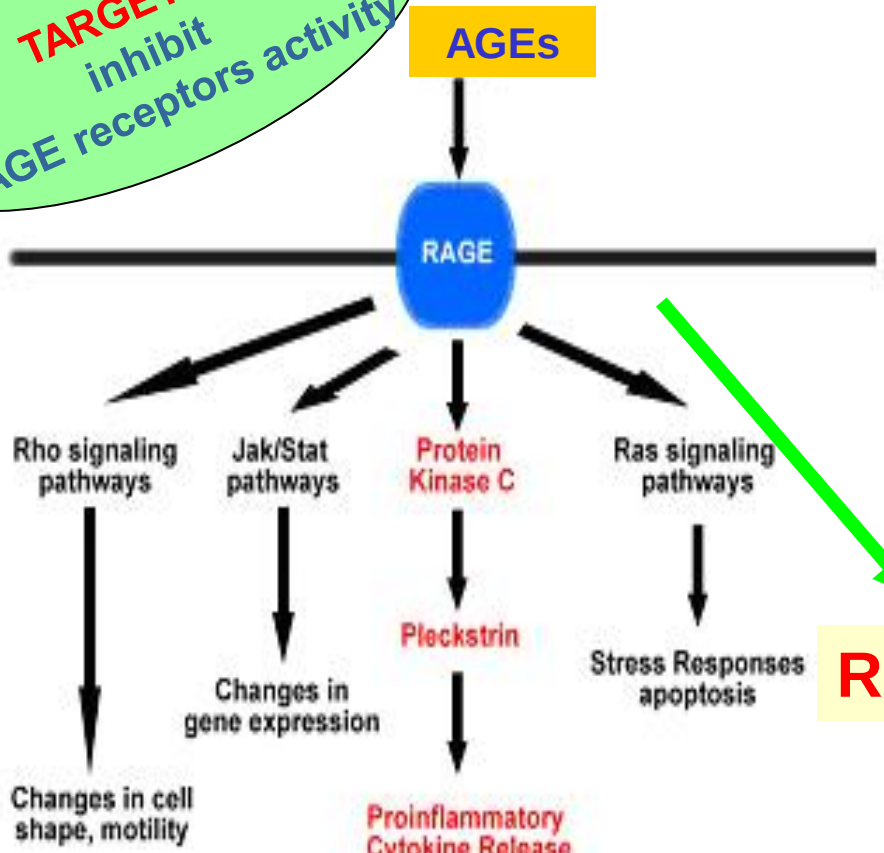
Effect of the pyridoindole antioxidant stobadine on development of experimental diabetic cataract and on lens protein oxidation in rats: comparison with vitamin E and BHT

Zuzana Kyselova,[1] Andrej Gajdosik,[1] Alena Gajdosikova,[1] Olga Ulicna,[2] Danica Mihalova,[1] Cimen Karasu,[3] Milan Stefek[1]

[1]Institute of Experimental Pharmacology, Slovak Academy of Sciences, Bratislava, Slovakia; [2]Pharmacobiochemistry Laboratory, 3rd Department of Internal Medicine, Faculty of Medicine, Comenius University, Bratislava, Slovakia; [3]Department of Pharmacology, Faculty of Medicine, Gazi University, Ankara, Turkey

AGE-R1 *versus* RAGE

TARGET !!!!
inhibit
RAGE receptors activity



ROS +

ERK/MAPK

INFLAMMAGING

the chief endocytic AGE receptor

ROS -

TARGET !!!!
increase
AGER receptors activity

Consumption of pomegranate polyphenols (PP) has already been demonstrated to suppress thyrozine oxidation to inhibit oxysterols production.

Punicic acid is an ω-5 long chain polyunsaturated fatty acid found in Punica granatum (pomegranate) seed oil, inhibits protein oxidation and carbonyl formation and ameliorate PKC signaling.

PP inhibits carbonyl production in diabetic animals, and ameliorate insulin signaling in INS1-E cells

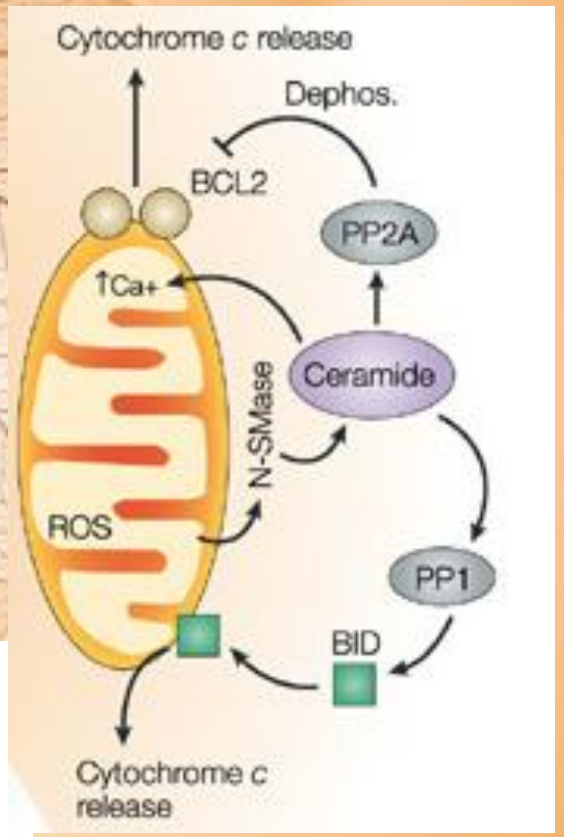
Grossman et al., 2010

Karasu et al., 2010

Diabetes-induced metabolic stresses lead to an upswing in production of a particular kind of fat molecule, known as ceramide

ceramide has a big effect on insulin resistance.

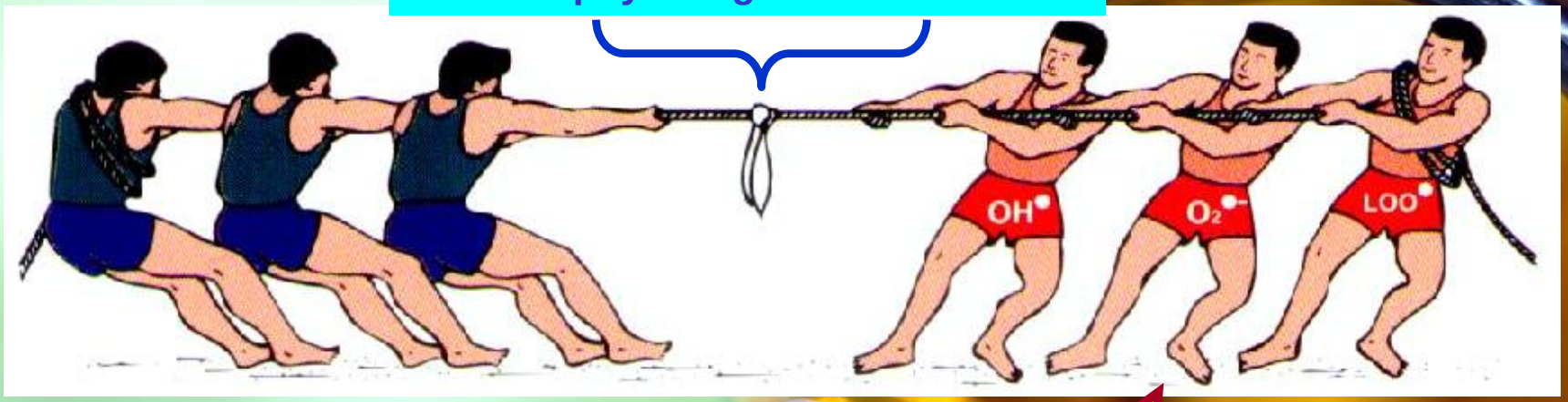
In some animal models, ceramide inhibition led to an almost complete restoration of insulin sensitivity.



Apoptosis 2005; 10: 841–850

Ceramide induces mitochondrial abnormalities in insulin-secreting INS-1 cells: Potential mechanisms underlying ceramide-mediated metabolic dysfunction of the β cell

baseline physiological levels of ROS

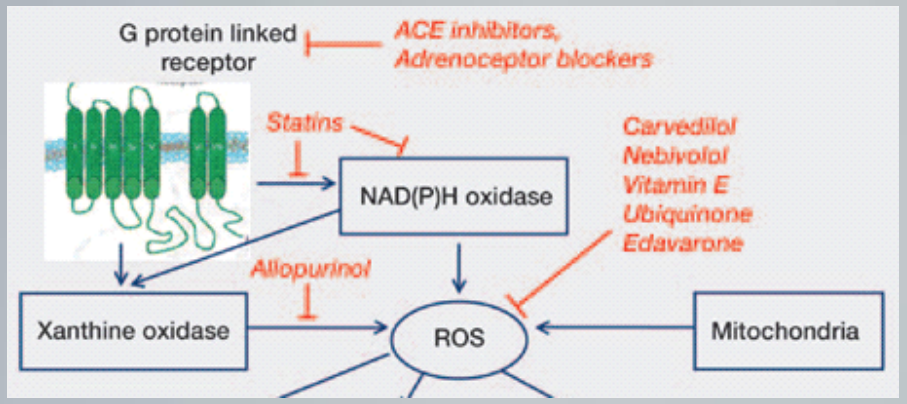


NATIVE PROTEIN

OXIDATION

REPAIR

DAMAGED PROTEIN



COULD HE LIVE TO 2150?

ANTIAGING COCKTAIL

Many scientists believe drugs that slow down aging will exist within 25 years

Anti-Aging Laboratory

- Nutrigenetic Profile
- Inflamation Profile
- Detoksification Profile
- Sport and Nutrition Profile
- Dermatological Genetic Profile
- Genes Releted to Oxidative Stress
- Genes Releted to Lipid Metabolism
- Genes related to glucose/insulin metabolism and physical activity
- Genes related to body mass index and the distribution of body fat
- Genes related to Metabolism
- Genes related to the hemodynamics of physical training responsiveness
- Osteoporosis Genetic profile
- Pharmacologic Genetic advanced profile
- Polymorphisms implied in risk of high blood pressure
- Polymorphisms implied in Endothelial vulnerability
- Polymorphisms implied in risk of Thrombosis
- AnttiiAgiing Genettiic advanced prroffiille
- Polymorphisms implied in risk of Environmental Stress, Nutrigenetic

WEIGHT CONTROL BASIC WeightGen

Weight Control Genetic profile: 11 genes and 13 polymorphisms of DNA .
CODE: WEIGHTG

Energy Expediture

ADRB1

ADBR2

ADBR3

Appetite

SR

Adipogenesis

ILbeta

IL1RN

IL6

PPARgamma

LPL (3 SNP's)

PLIN

FABP2

BUSH AS BUSINESSMAN • HORMONE THERAPY RISKS

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THE INTERNATIONAL NEW

SPECIAL DOUBLE ISSUE

July 22/July 29, 2002

Women were told for decades that hormone-replacement therapy would protect their hearts and preserve their youth. Now the evidence is in, and an era is over.

THE END OF THE AGE OF ESTROGEN

BY GEOFFREY COWLEY AND KAREN SPRINGEN

MENOPAUSE MAY BE A NATURAL event, but the medical establishment has never viewed it as an auspicious one. "The years of the climacteric are the most troublesome in married life," the Czechoslovakian physician Arnold Lorand declared in his 1910 classic "Old Age Deferred"—"not only for the wife, who is directly affected by it, but also in almost equal degree for the husband, who must show the greatest forbearance." Luckily there was good news for the menopausal woman, "if only she be a clever member of her sex." Lorand had discovered that extracts from pigs' ovaries could "put off old age for a score of years," or at least "mitigate its effects when it has asserted itself with all its terrors." By the early 1940s, drugmakers were mass-producing estrogen from pregnant mares' urine (hence the brand name Premarin). And by 1960 the august New England Journal of Medicine was rec-

The Study

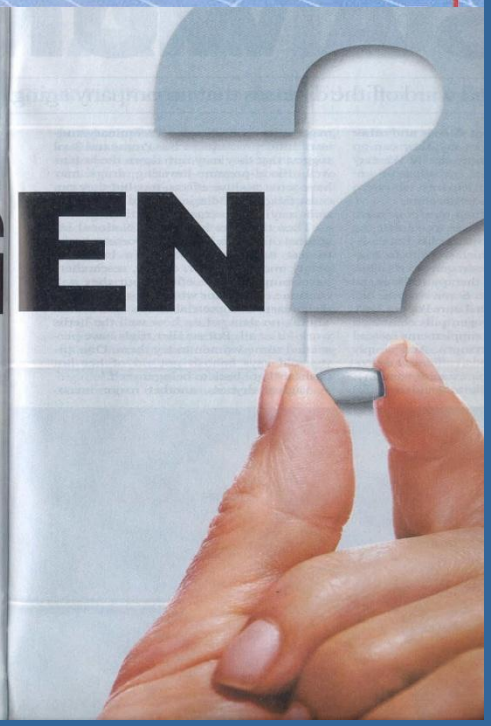
Among 10,000 users of hormone-replacement therapy there were:

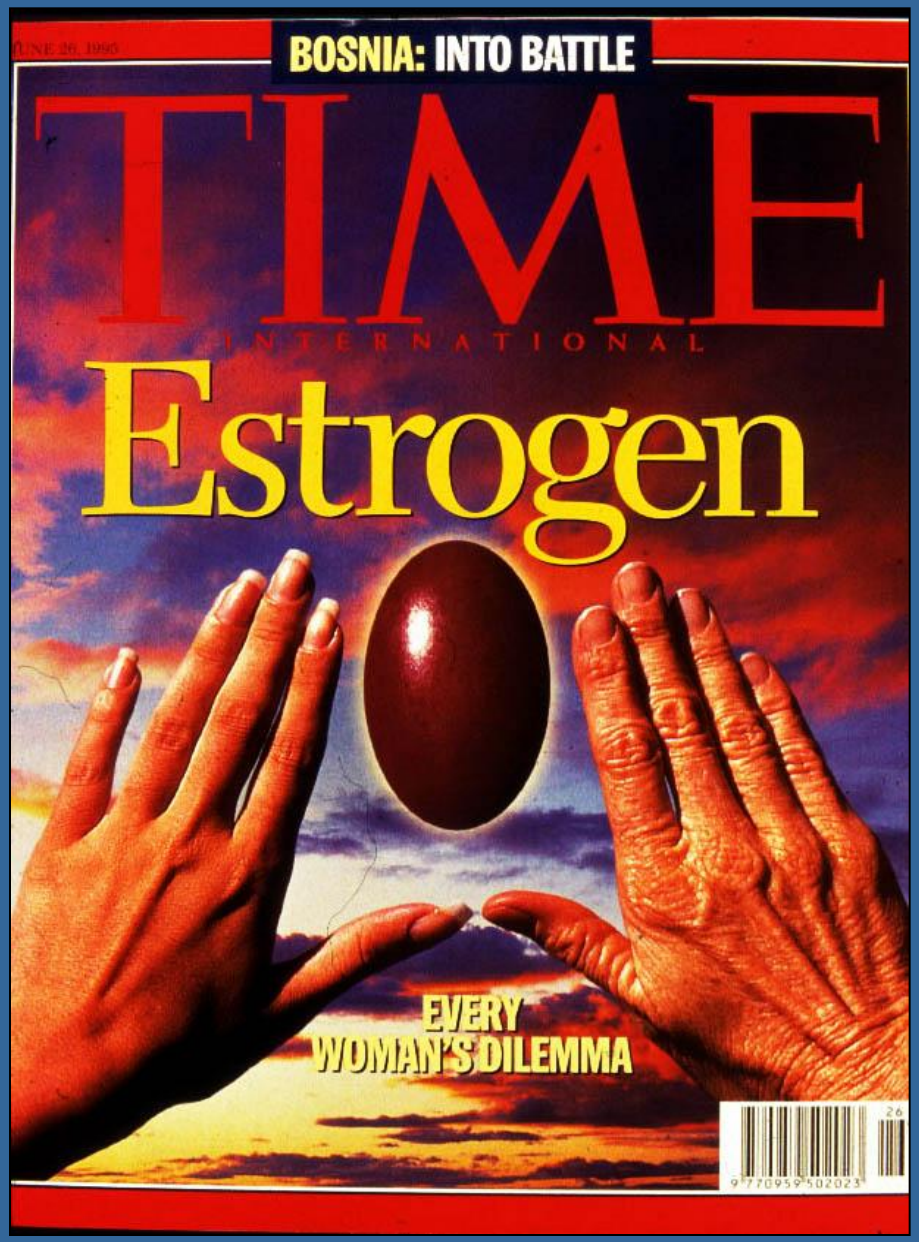
MORE
+7 Heart attacks
+8 Strokes
+8 Breast cancers
+8 Blood clots

FEWER

This wasn't just another isolated study contradicting the last one to make headlines. U.S. health officials announced last Tuesday that the jury was finally in—and that Prempro does significantly more harm than good when taken for long periods. Women had been told for decades that estrogen taken with progestin would not only ease hot flashes and insomnia but help preserve bone strength, mental acuity and, most important, heart health. There's no question that HRT can ease the acute symptoms of menopause, and the claim about bone strength has held up to scrutiny. But after following more than 16,000 women for roughly five years, researchers found conclusively that the hormones in Prempro raise the risk of heart attack, stroke, blood clots and breast cancer. Dr. JoAnn Manson, a women's health expert at Harvard Medical School, calls it "the most dramatic sea change I've seen in clinical medicine."

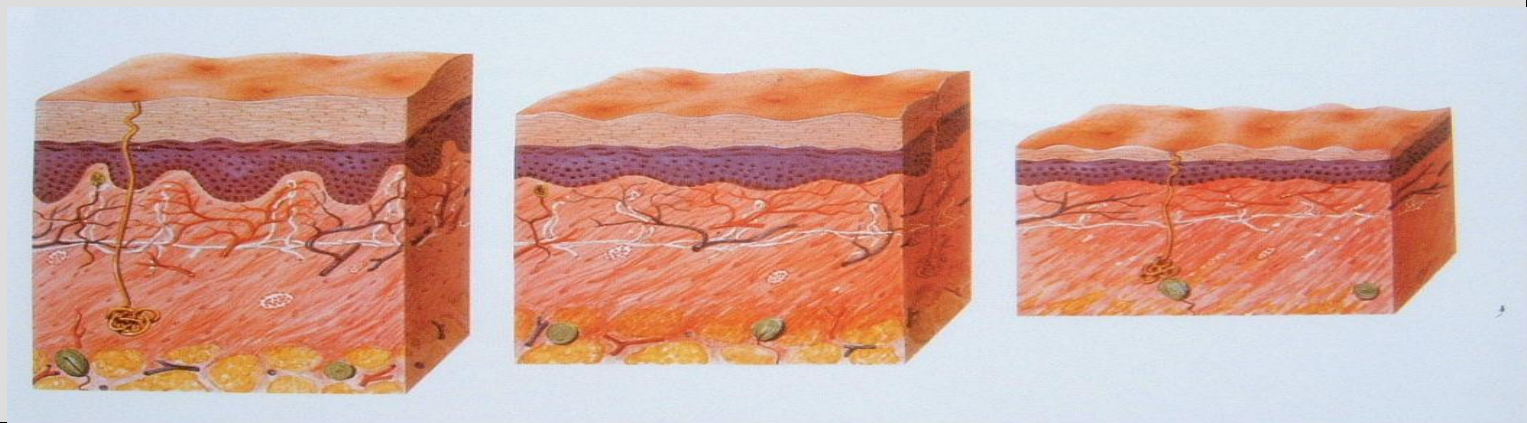
The findings don't rule out Prempro as a short-term remedy for menopausal symptoms. And they don't apply to women who take estrogen without progestin following hysterectomy. But for millions of women juggling the pros and cons of long-term HRT, the new findings offer something virtually unprecedented—clarity. Until recently, the available research suggested that long-term HRT was a boon to women's health. When scientists followed large groups of women through their later years, the hormone users always seemed to fare best. Those on long-term treatment suffered more than their share of breast cancer, but they





The dilemma of hormone replacement therapy is not a dilemma of the hormones, not a dilemma of oestrogen, it is a dilemma of bad clinical practice and of the wrong prescribing rate of hormones and this should be changed in the future.

Skin ageing



Scientific Instututions, Foundations, Associations & Societies on Anti-Aging/Longevity Sciences

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Rooms 1 | Adults per room 1
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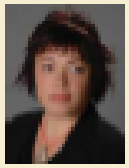
The comprehensive conference program ensures the coverage of all components of Anti-Aging science and includes lectures on longevity philosophy, age management, weight management, nutrition-nutrigenetics & genomics for Anti-Aging medicine, preventive, regenerative, integrative medicine for longer health span, detoxification & stress management, and cosmetology science complemented by information presented in the exhibition hall.

The congress will consist of informative sessions, interactive discussions and workshops which will be conducted by many distinguished scientists.

We look forward to welcoming you, clinicians, scientists, visitors and exhibitors to Istanbul in May 2012.

Sincerely Yours ,

Prof. Dr. Çimen Karasu
President 3rd ECOPRAM



Prof. Dr. Christos Zouboulis
President ESAAM

ESAAM

ECOPRAM
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Prof. Dr. Çimen KARASU

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