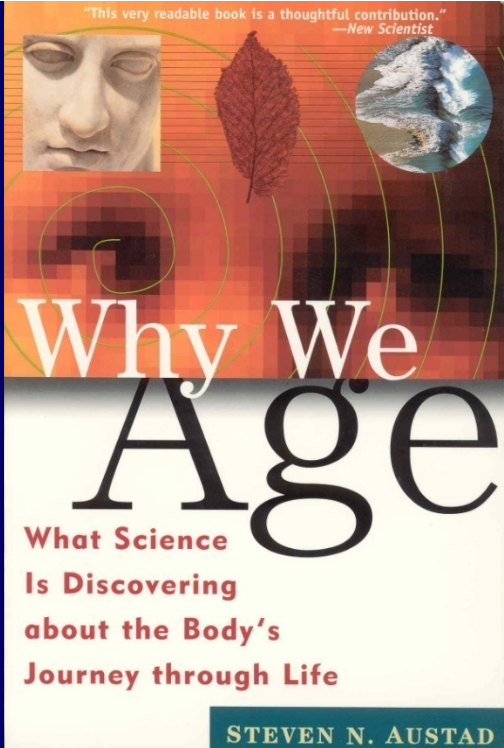
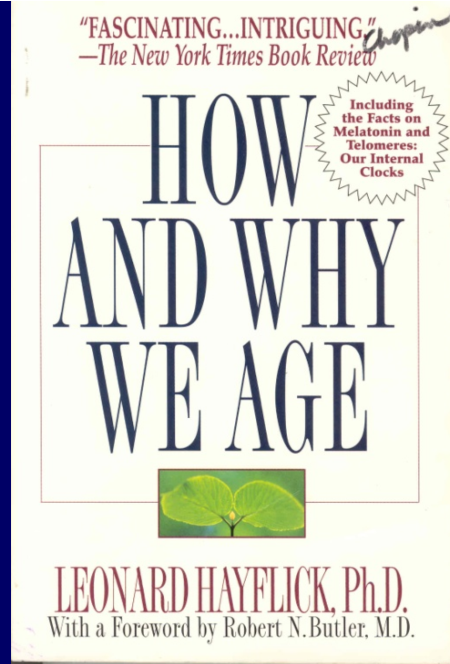
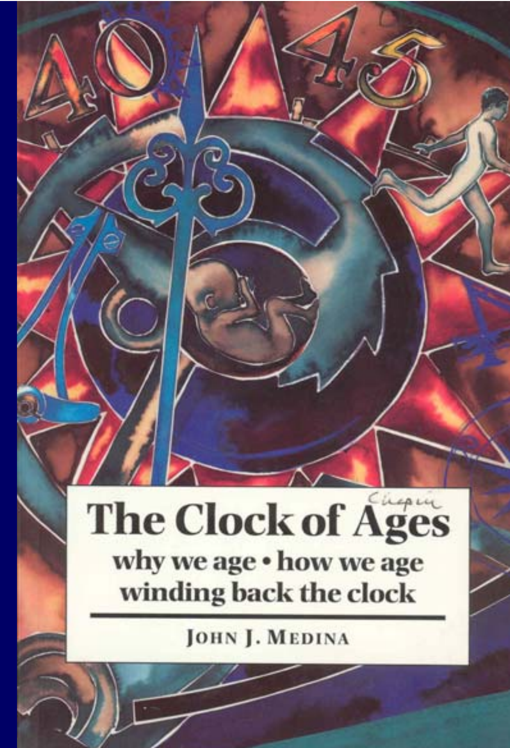
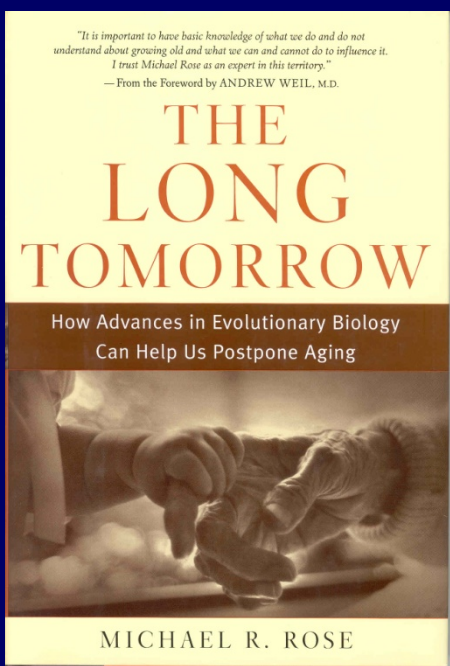
Stress ossidativo e invecchiamento

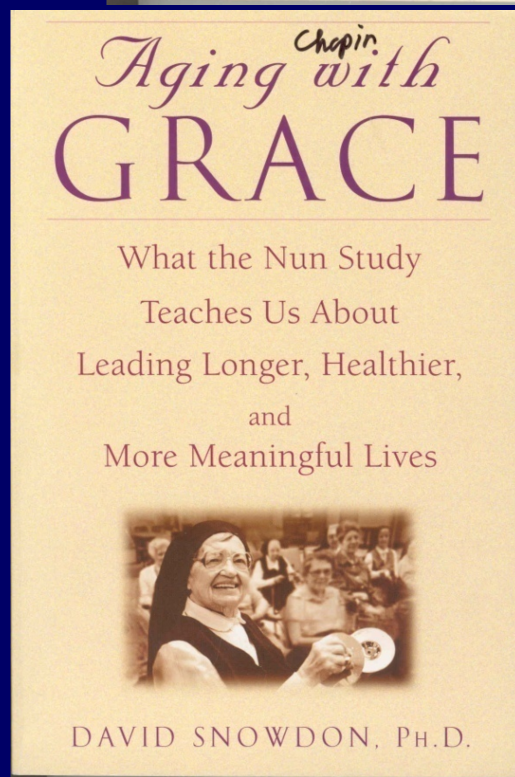
Gianluigi Vendemiale

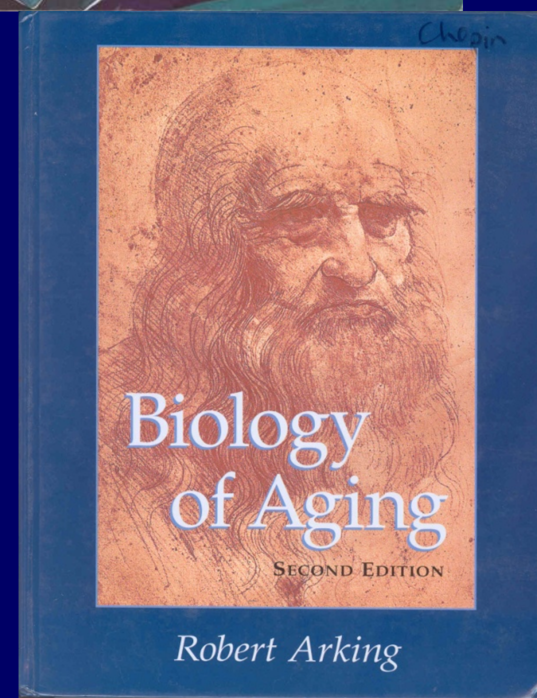

"This very readable book is a thoughtful contribution."
—New Scientist
Why We Age
What Science Is Discovering about the Body's Journey through Life
STEVEN N. AUSTAD


"FASCINATING...INTRIGUING"
—The New York Times Book Review
Chapin
HOW AND WHY WE AGE
Including the Facts on Melatonin and Telomeres: Our Internal Clocks
LEONARD HAYFLICK, Ph.D.
With a Foreword by Robert N. Butler, M.D.


40
45
The Clock of Ages
Chapin
why we age • how we age
winding back the clock
JOHN J. MEDINA


"It is important to have basic knowledge of what we do and do not understand about growing old and what we can and cannot do to influence it. I trust Michael Rose as an expert in this territory."
— From the Foreword by ANDREW WEIL, M.D.
THE LONG TOMORROW
How Advances in Evolutionary Biology Can Help Us Postpone Aging
MICHAEL R. ROSE


Aging with GRACE
Chapin
What the Nun Study Teaches Us About Leading Longer, Healthier, and More Meaningful Lives
DAVID SNOWDON, PH.D.


Chapin
Biology of Aging
SECOND EDITION
Robert Arking

THEORIES OF AGING

Cross Linkage

Neuroendocrine

Telomeres

Immune

Somatic Mutation

Genetic

Waste accumulation/Lipofuscin

Oxidative Damage

THEORIES OF AGING

The Free Radical Theory of Aging
D. Harman 1956

Repair

- Genetic

(Hayflick and Moorhead, 1961)

RADICALI LIBERI

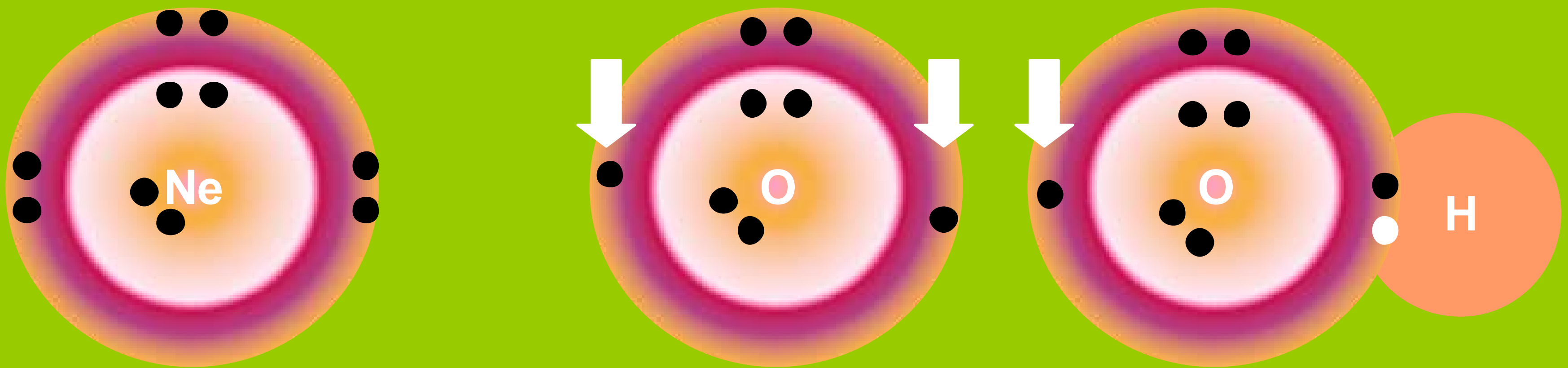
A^{+} B^{-} **Ioni**

A : B

$A^{\bullet}$ $B^{\bullet}$ **Radicali Liberi**

Atomi o molecole con un elettrone spaiato nell'orbitale esterno

Specie chimiche radicaliche



L'atomo di Ne
Solo elettroni appaiati

Atomo (stabile)

L'atomo di O
Due elettroni spaiati

Il radicale idrossile ($HO^{\cdot}$)
Un elettrone spaiato

Radicali liberi dell'ossigeno (instabili)

I radicali liberi, al contrario degli atomi, possiedono *sempre* elettroni spaiati

Formazione dei RL

Reattiva → **Difese organiche**

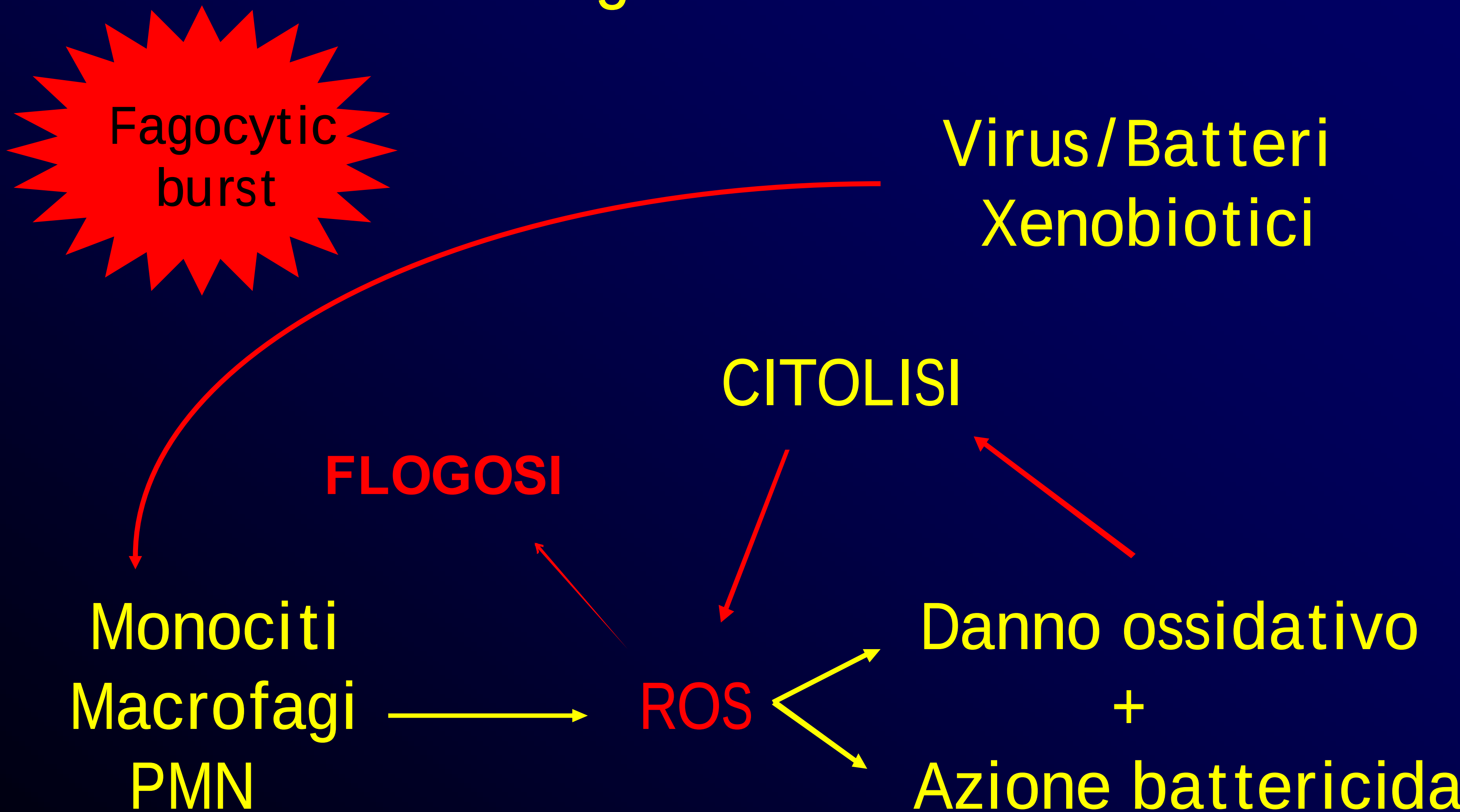
Energetica → **Radiazioni**

Ipossica → **Ischemia/Riperfusione**

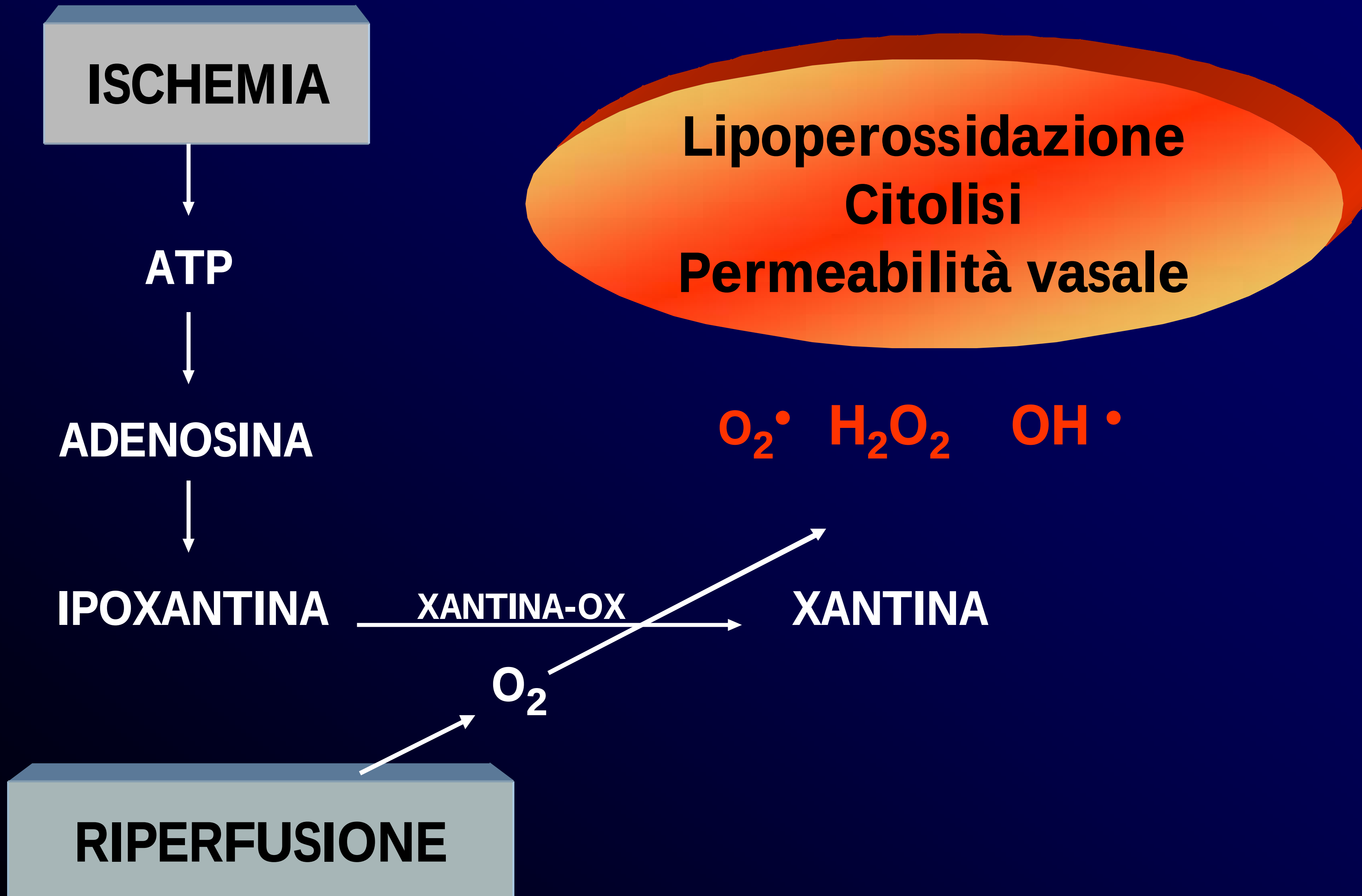
Metabolica → **Ossigeno**

Formazione dei RL

Reattiva: difese organiche

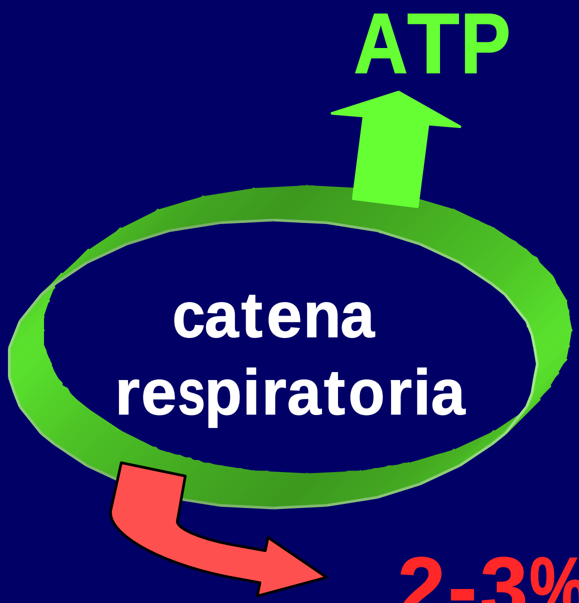


FENOMENO ISCHEMIA/RIPERFUSIONE



Formazione dei RL

METABOLICA → 95% O_2 →



2-3% ROS

$$O_2 \xrightarrow[e^-]{} O_2^- \xrightarrow[e^-\ 2H^+]{} H_2O_2 \xrightarrow[e^-\ H^+]{} OH^\bullet \xrightarrow[e^-\ H^+]{} H_2O$$

AUTOSSIDAZIONE/PEROSSIDAZIONE

$\downarrow$

Ossidazione di materiale organico con ossigeno atmosferico

$\downarrow$

REAZIONE A CATENA

$\downarrow$

$$RH$$

$\downarrow$

$$R^{\bullet}$$

$\downarrow$

$$ROOH + R^{\bullet} \longleftarrow ROO^{\bullet} \longrightarrow 2RO^{\bullet} + O_2$$

$$ROOH + R^{\bullet} \longrightarrow RO^{\bullet} + OH^{\bullet} \longrightarrow ROH + R^{\bullet}$$

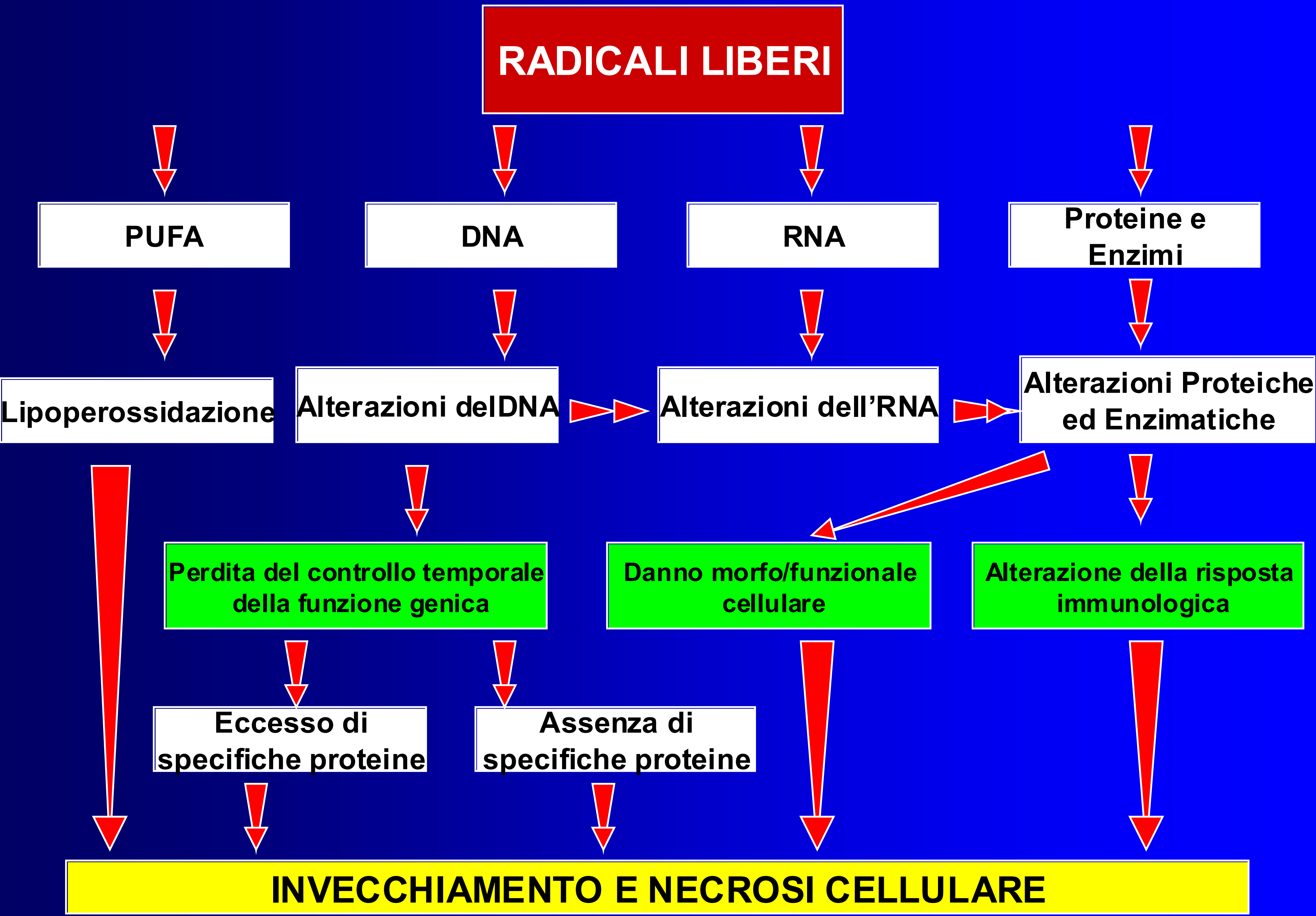
$$ROO^{\bullet} \longrightarrow 2RO^{\bullet} \longrightarrow ROH + R^{\bullet}$$

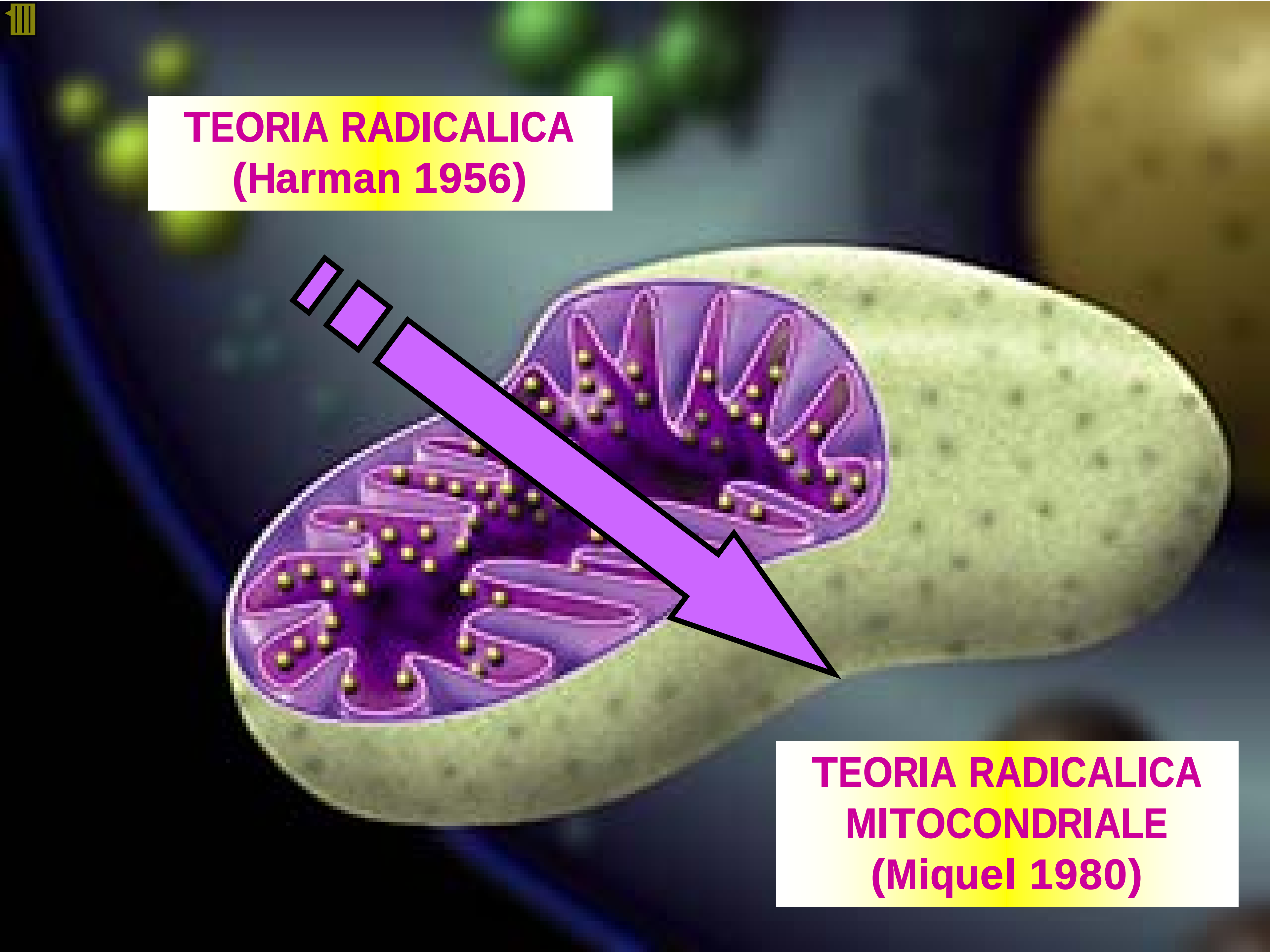
The Free Radical Theory of Ageing

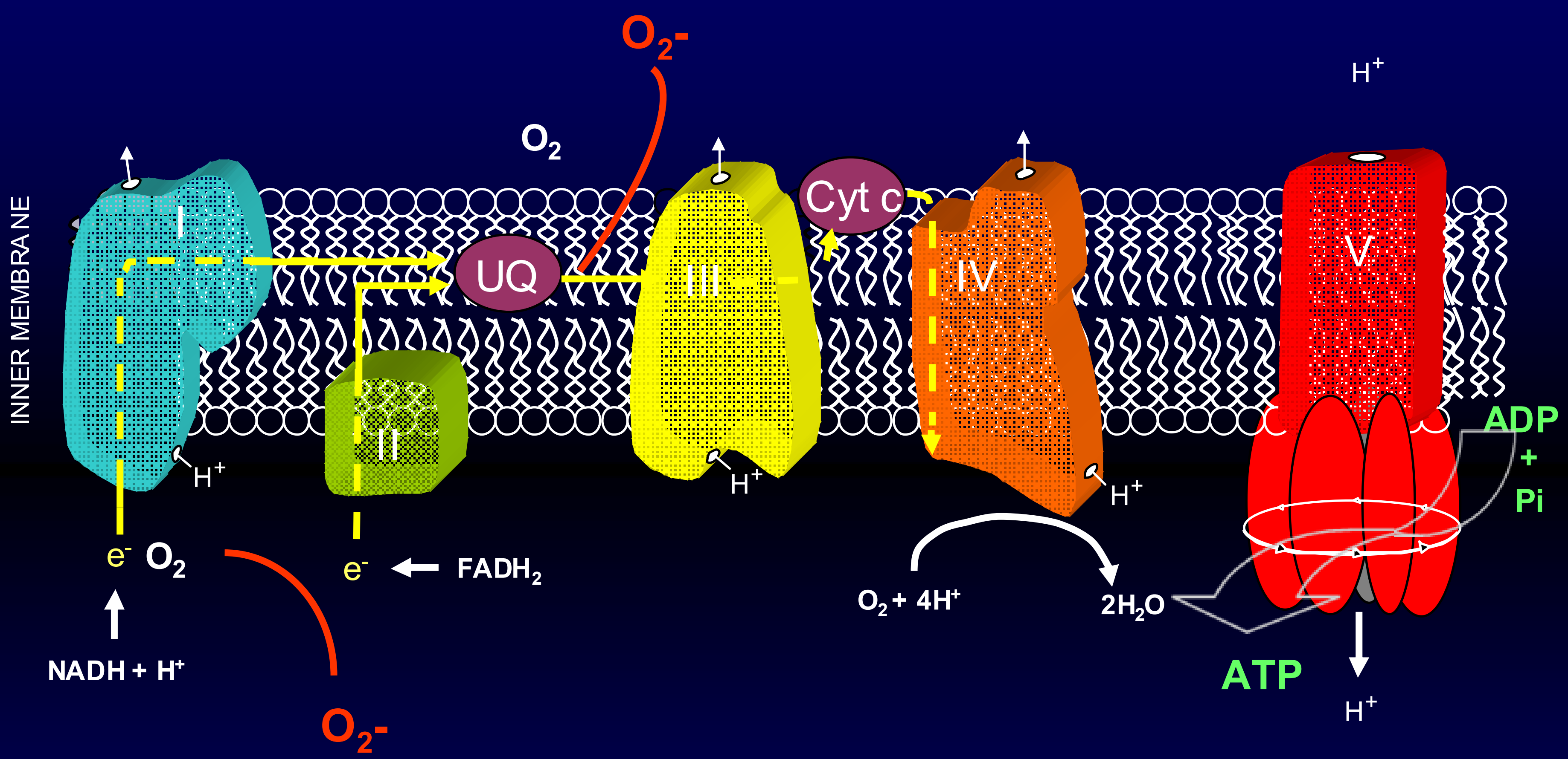
L'invecchiamento cellulare è "*il prodotto della serie di reazioni ossidative di natura radicalica cui si è necessariamente esposti per il semplice fatto di utilizzare l'ossigeno….la longevità dipende dall'efficienza dei sistemi di protezione antiossidante*"

Harman D. J Gerontol 1956

L'ossigeno, questo caro indispensabile criminale

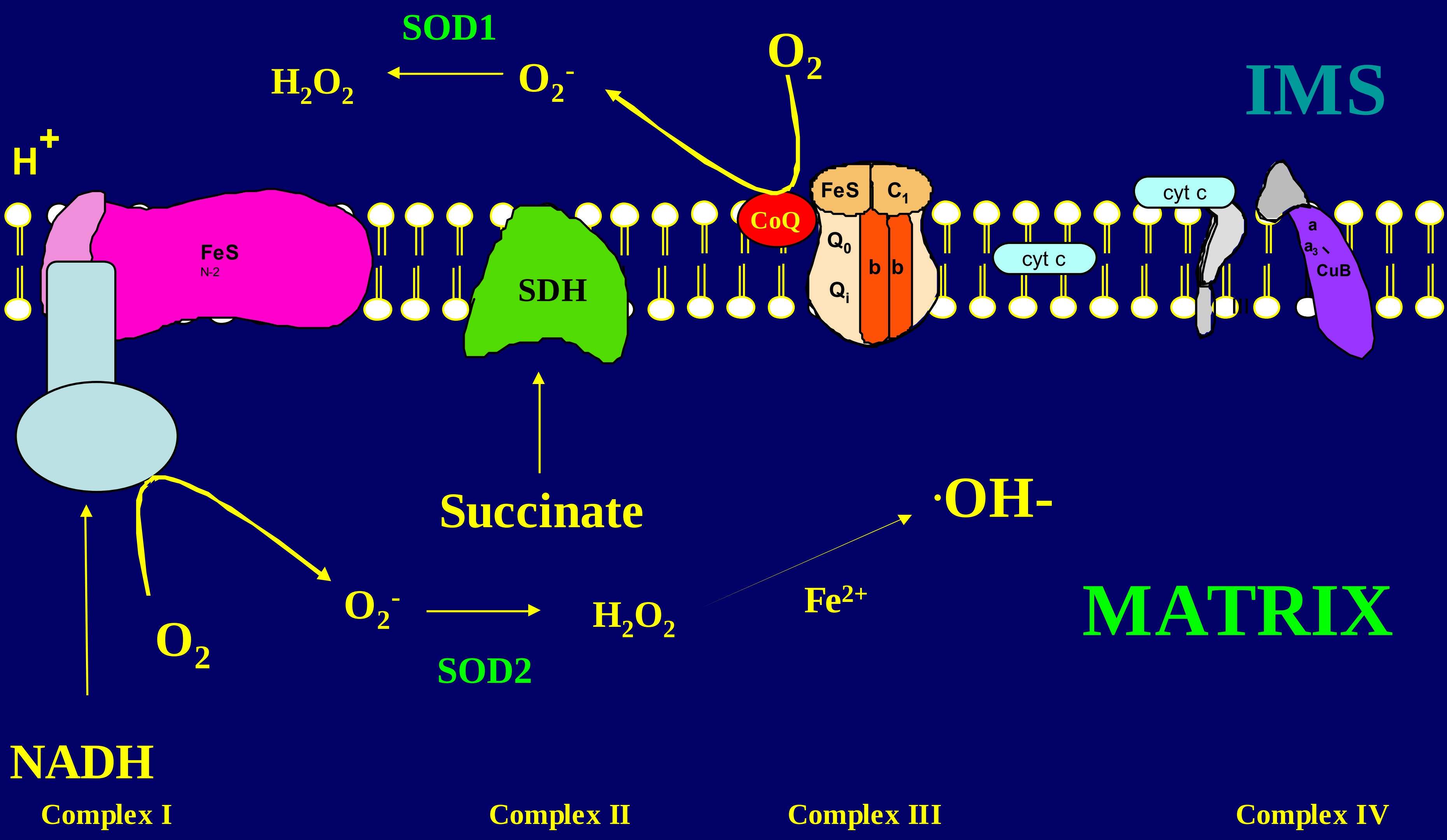

RADICALI LIBERI
PUFA
DNA
RNA
Proteine e Enzimi
Lipoperossidazione
Alterazioni delDNA
Alterazioni dell'RNA
Alterazioni Proteiche ed Enzimatiche
Perdita del controllo temporale della funzione genica
Danno morfo/funzionale cellulare
Alterazione della risposta immunologica
Eccesso di specifiche proteine
Assenza di specifiche proteine
INVECCHIAMENTO E NECROSI CELLULARE


TEORIA RADICALICA
(Harman 1956)
TEORIA RADICALICA
MITOCONDRIALE
(Miquel 1980)



The Mitochondrial Electron Transport System

Reactive Oxygen species and the Respiratory Chain



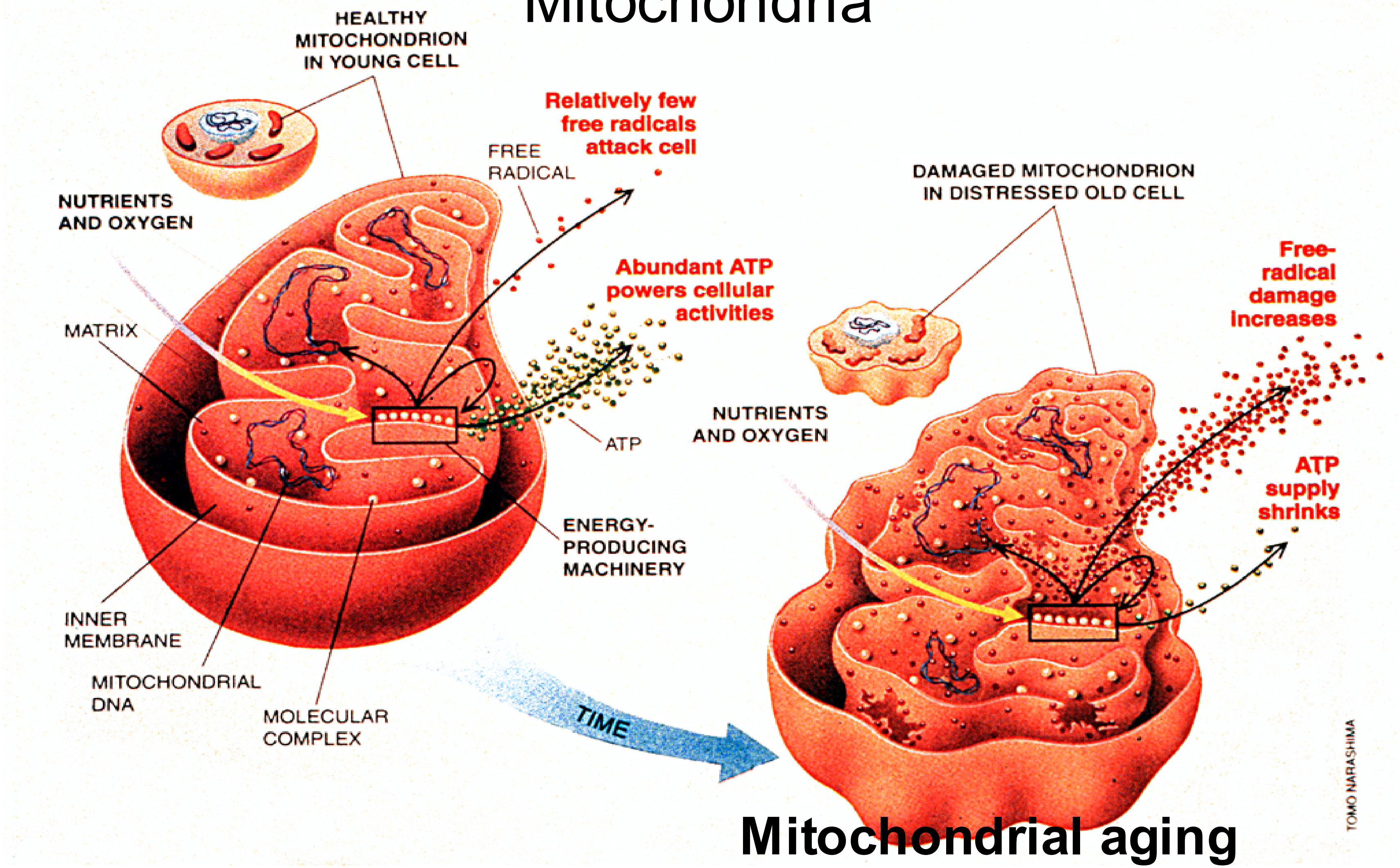
The continuous generation of ROS by mitochondria throughout cell life produces an age related chronic oxidative stress on mtDNA…

…mtDNA is specially susceptible to oxidative damage because it lacks protective histones and has no introns…

…This damage includes single and double strand breaks, deletions, base changes, chromosomal aberrations up to transcription of mitochondrial genes…

Miquel J et al. Exp Gerontol 1980
Halliwell and Aruoma FEBS Lett 1991
Kristal BA et al. Free Rad Biol Med 1994

Oxidative Stress and Aging: A critical Role for Mitochondria



Mitochondrial aging

↓

Cell aging

Sistemi di difesa antiossidante

Primari
Preventive antioxidant

Prevengono l'inizio della cascata di reazioni

1. Chelanti dei metalli di transizione (Fe-Cu)
2. Ortoidrossibenzofenoni
3. Composti solfonati
4. Enzimi (SOD-CAT)
5. Flavonoidi

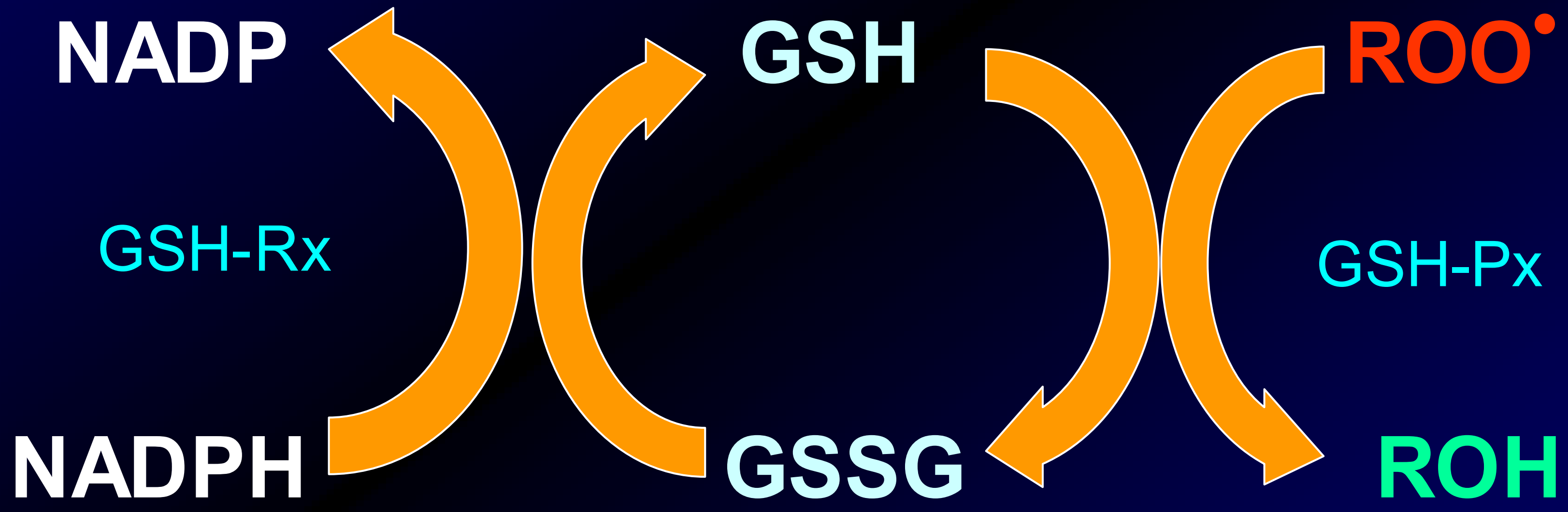
Secondari
Chain breaking antioxidant

Interferiscono con la propagazione delle reazioni

1. Glutatione e precursori (NAC, SAMe)
2. Polifenoli (flavonoidi, procianidine)
3. Vitamine (C, E)
4. Enzimi (GSH-Px, GSH-Tf)

GLUTATIONE

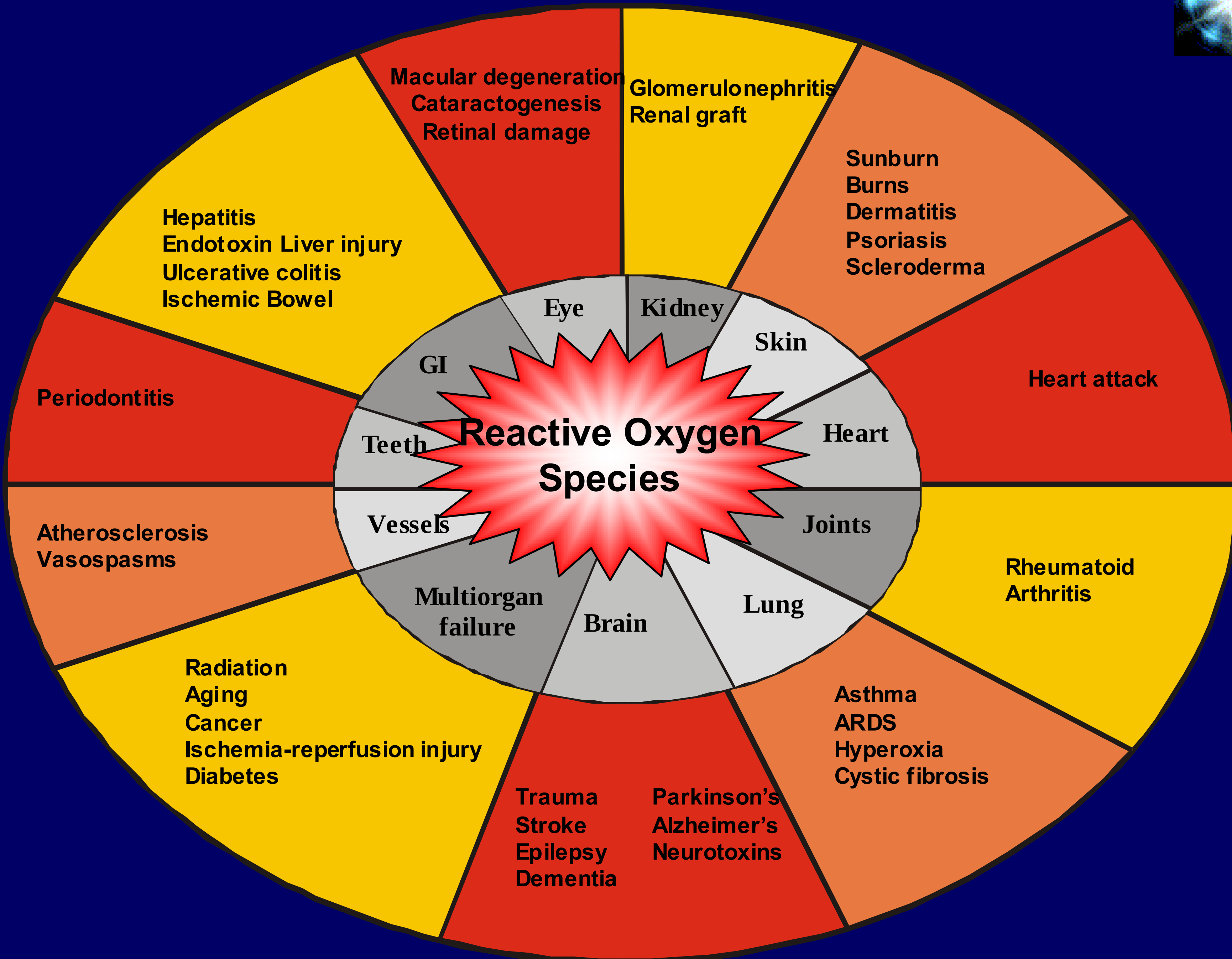
gamma-glutamil-cisteinil-glicina



↑ FATTORI PRO-OSSIDANTI

STRESS OSSIDATIVO

↓ BARRIERA ANTI-OSSIDANTE

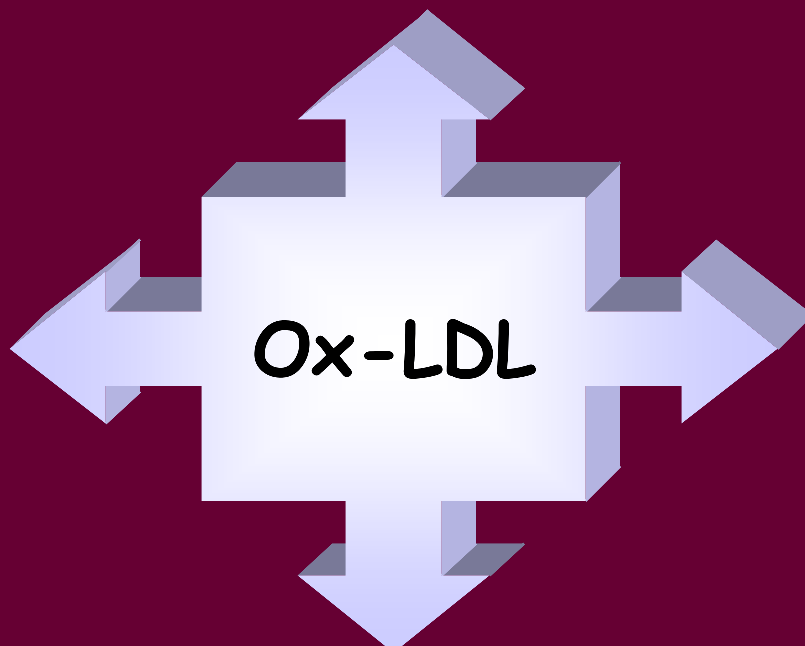

Reactive Oxygen Species
Eye
Kidney
Skin
Heart
Joints
Lung
Brain
Multiorgan failure
Vessels
Teeth
GI
Macular degeneration
Cataractogenesis
Retinal damage
Glomerulonephritis
Renal graft
Sunburn
Burns
Dermatitis
Psoriasis
Scleroderma
Heart attack
Rheumatoid Arthritis
Asthma
ARDS
Hyperoxia
Cystic fibrosis
Trauma
Stroke
Epilepsy
Dementia
Parkinson's
Alzheimer's
Neurotoxins
Radiation
Aging
Cancer
Ischemia-reperfusion injury
Diabetes
Atherosclerosis
Vasospasms
Periodontitis
Hepatitis
Endotoxin Liver injury
Ulcerative colitis
Ischemic Bowel

L’ATEROSCLEROSI

ATEROSCLEROSI: RUOLO DELLE OX-LDL

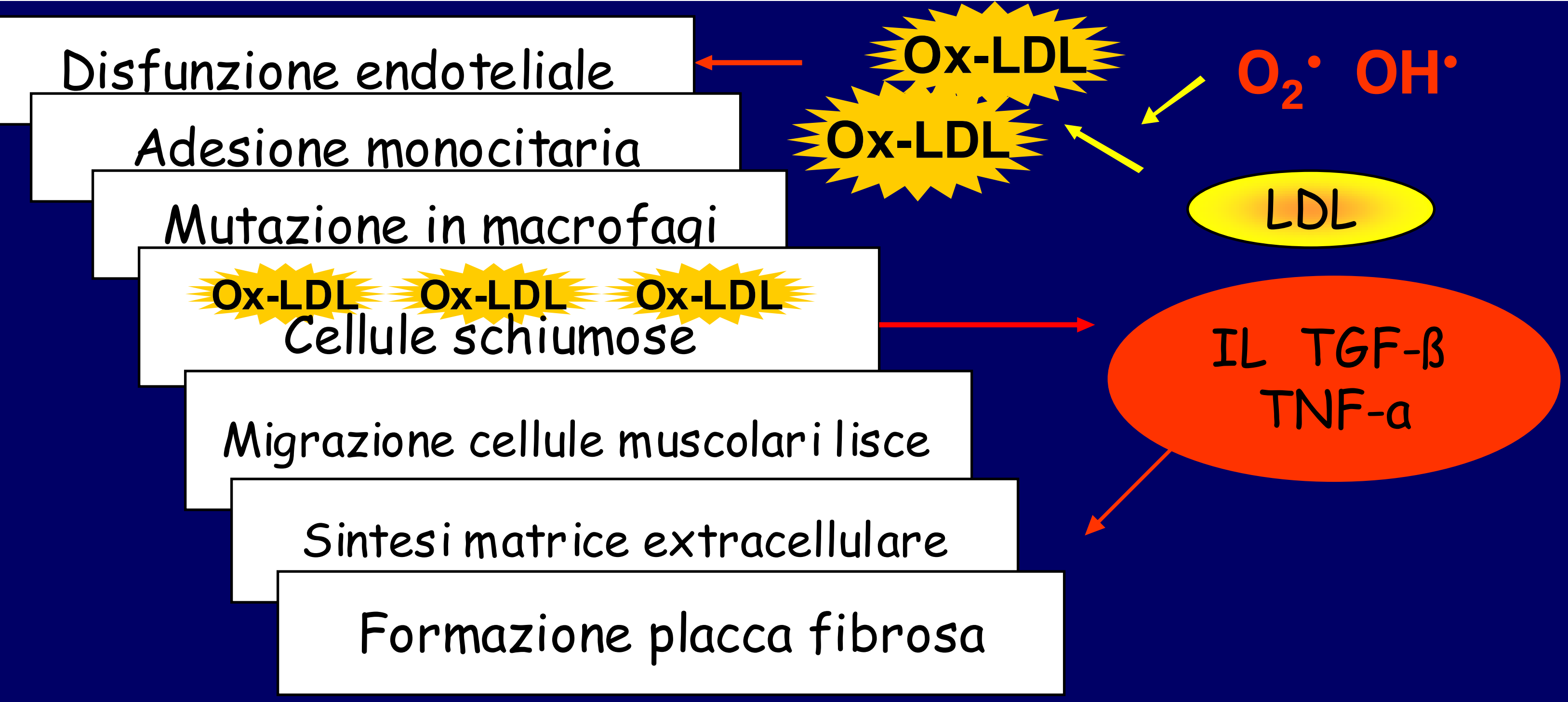
Effetto pro-infiammatorio
chemiotattico sui monociti

Formazione di
Cellule schiumose

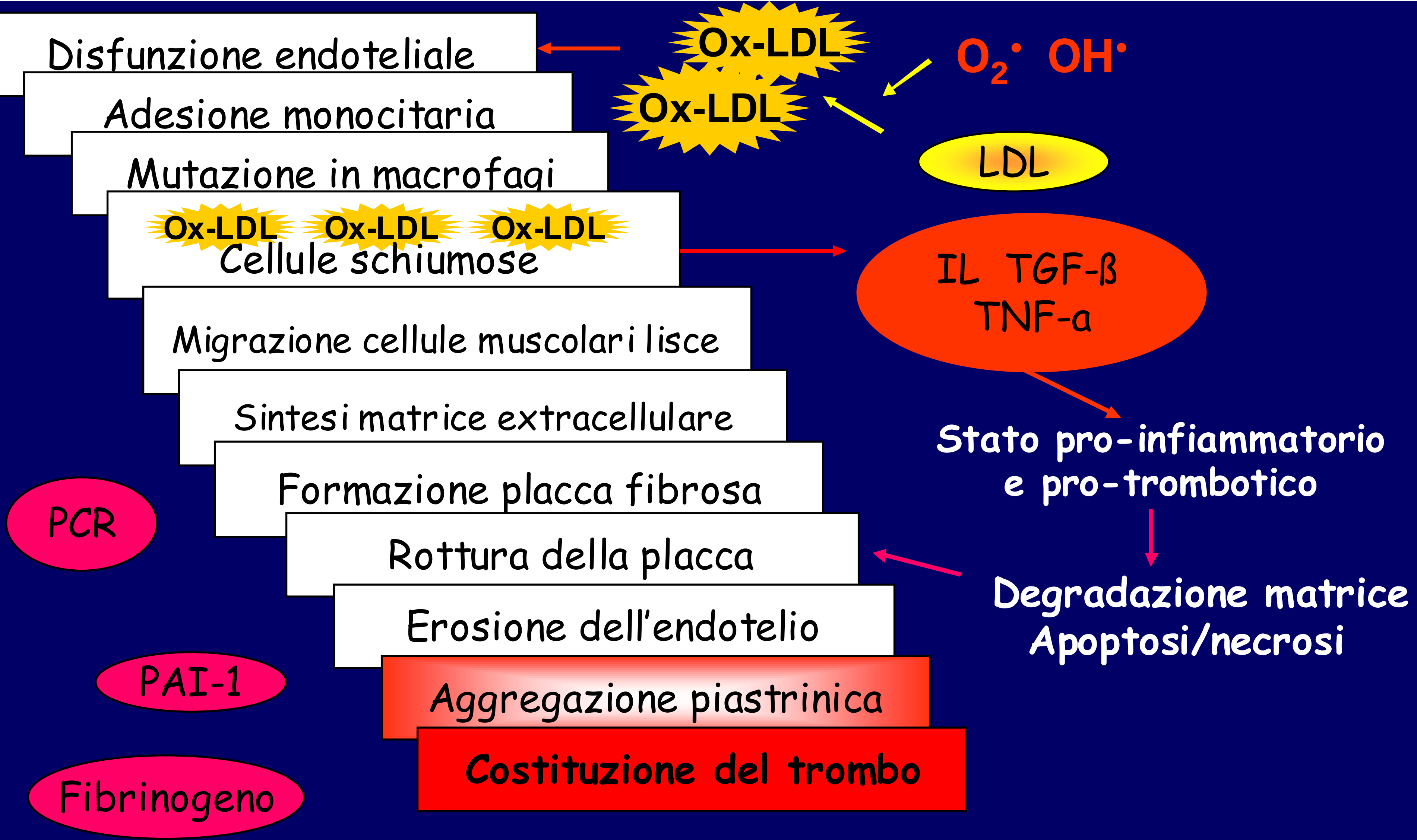


Immunogenicità
Citotossicità

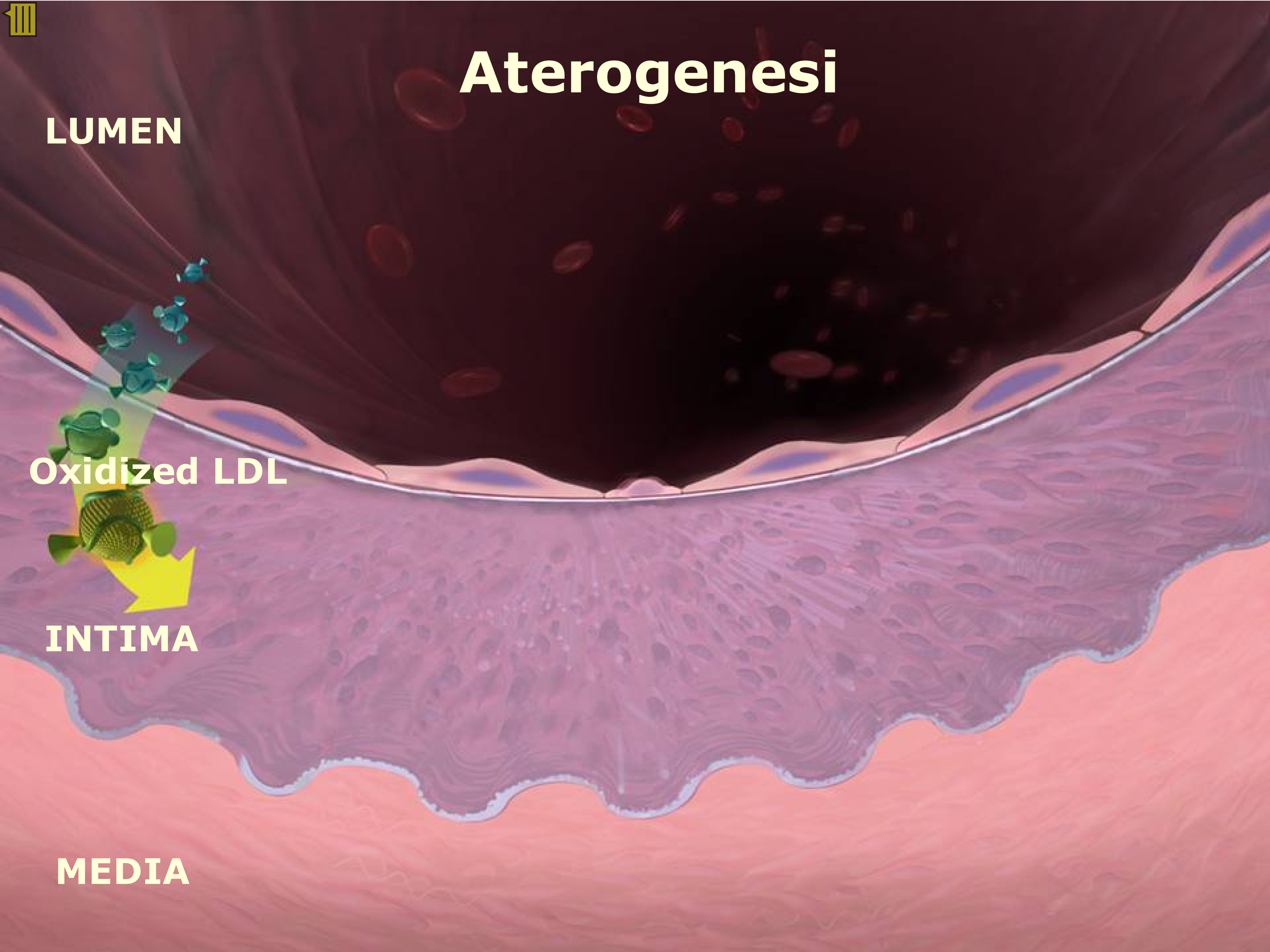
Inibizione della vasodilatazione
NO-mediata



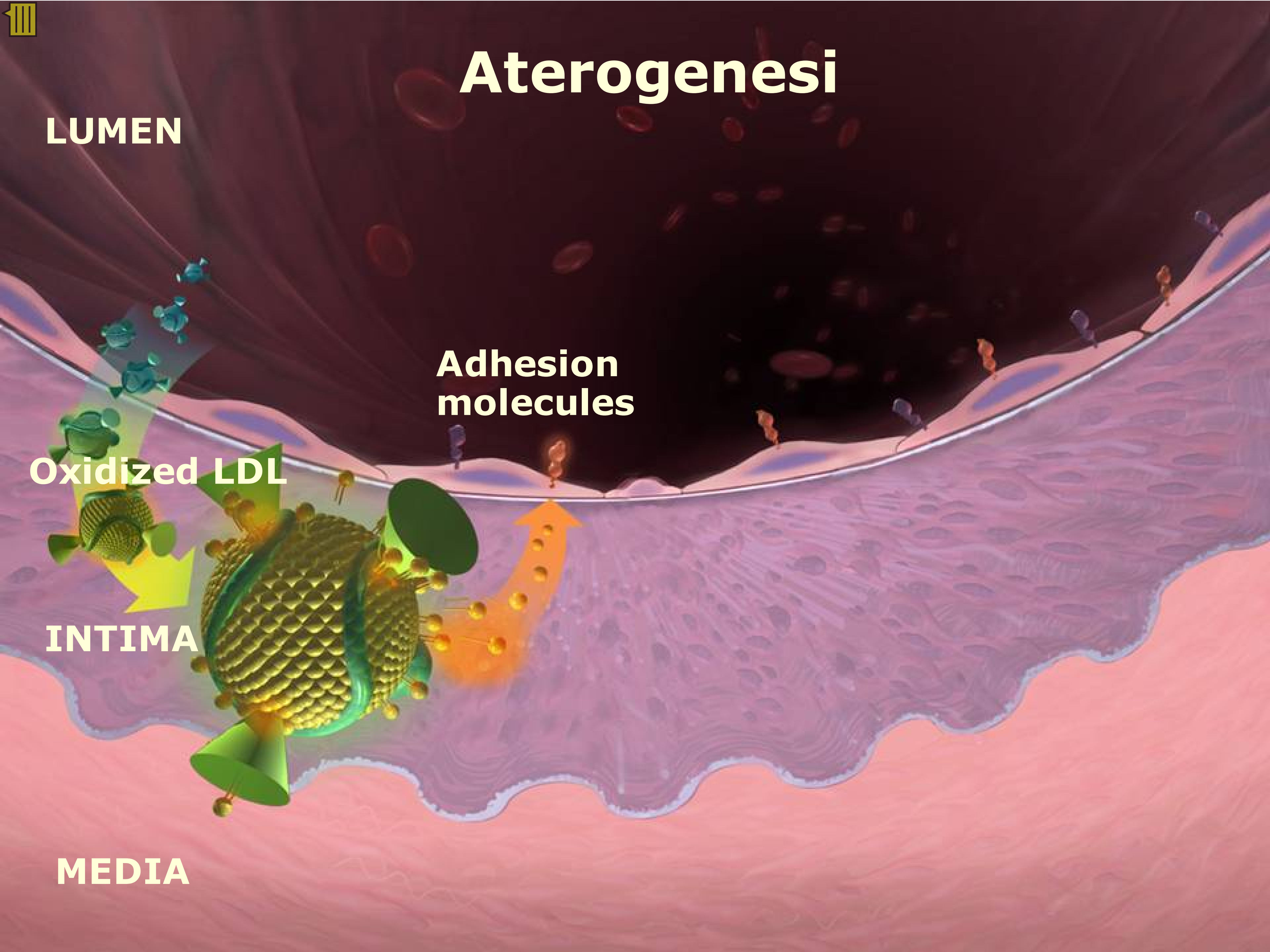
Disfunzione endoteliale
Adesione monocitaria
Mutazione in macrofagi
Ox-LDL Ox-LDL Ox-LDL
Cellule schiumose
Migrazione cellule muscolari lisce
Sintesi matrice extracellulare
Formazione placca fibrosa
Ox-LDL
Ox-LDL
$O_2^{\bullet}$ $OH^{\bullet}$
LDL
IL TGF-ß
TNF-a


Disfunzione endoteliale
Adesione monocitaria
Mutazione in macrofagi
Ox-LDL
Ox-LDL
Ox-LDL
Cellule schiumose
Migrazione cellule muscolari lisce
Sintesi matrice extracellulare
Formazione placca fibrosa
Rottura della placca
Erosione dell'endotelio
Aggregazione piastrinica
Costituzione del trombo
Ox-LDL
Ox-LDL
$O_2^{\bullet}$ $OH^{\bullet}$
LDL
IL TGF-ß
TNF-a
Stato pro-infiammatorio
e pro-trombotico
Degradazione matrice
Apoptosi/necrosi
PCR
PAI-1
Fibrinogeno

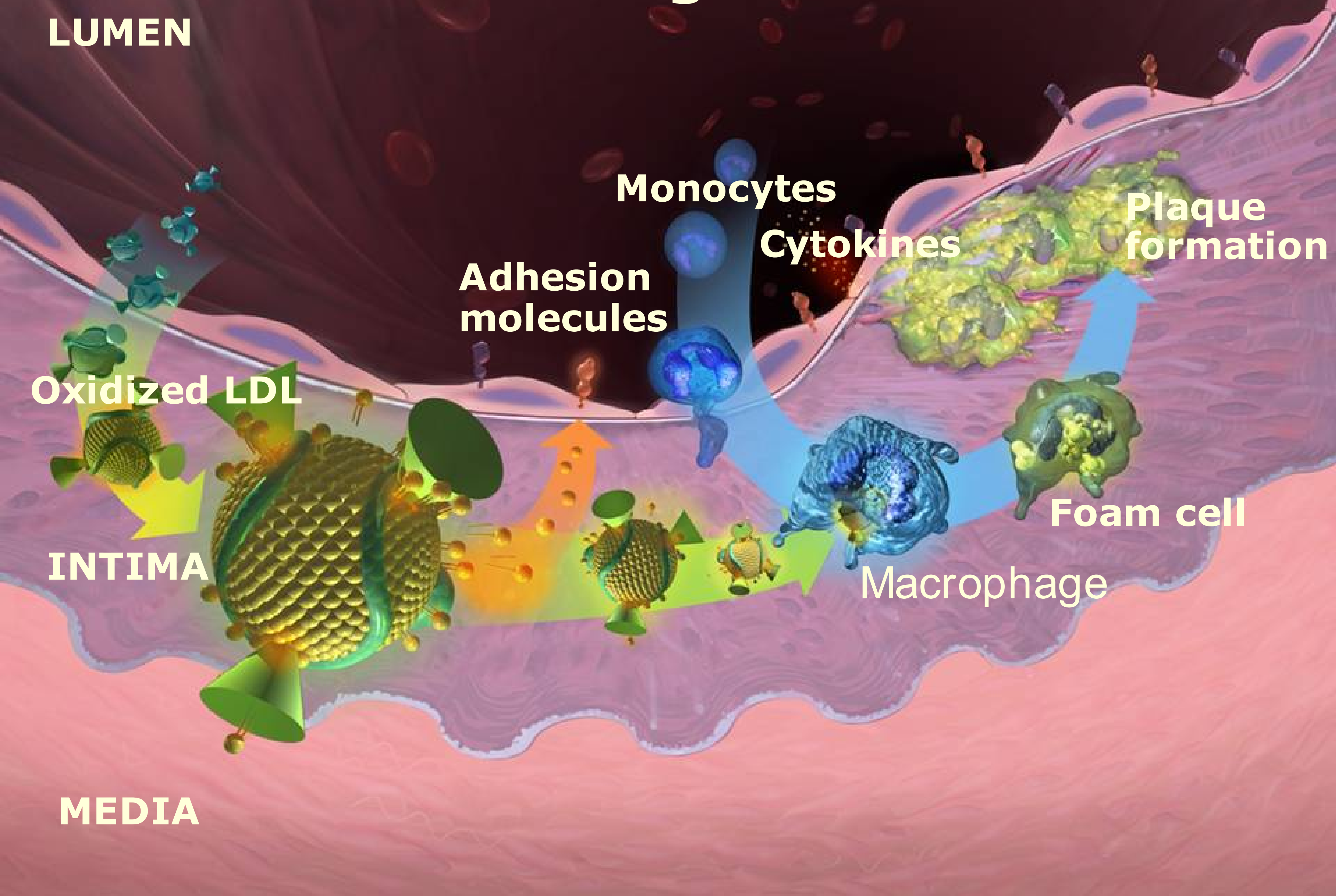
Aterogenesi

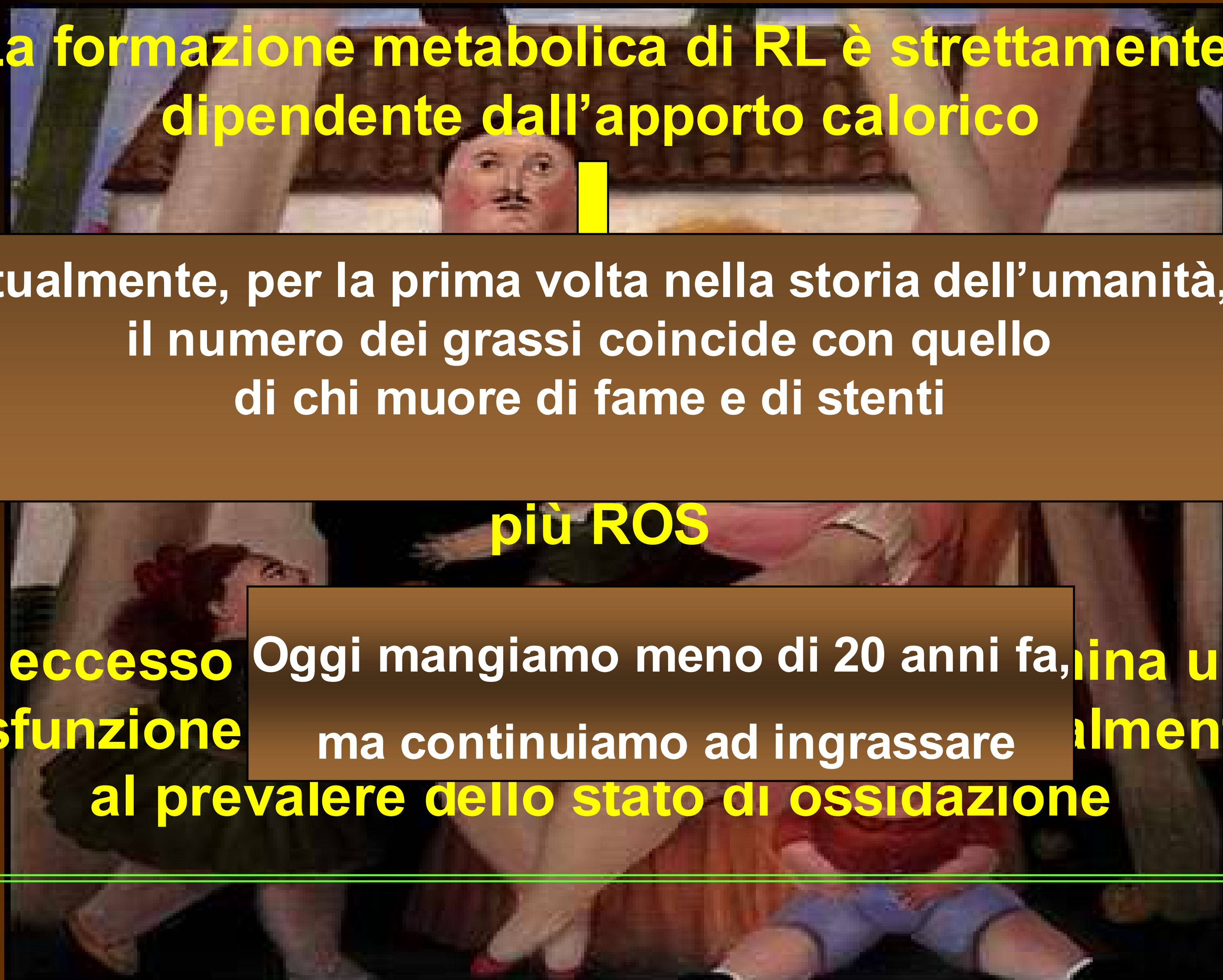


Aterogenesi



Aterogenesi





La formazione metabolica di RL è strettamente dipendente dall'apporto calorico

Attualmente, per la prima volta nella storia dell'umanità, il numero dei grassi coincide con quello di chi muore di fame e di stenti

la

,

a

più ROS

Oggi mangiamo meno di 20 anni fa, ma continuiamo ad ingrassare

Un eccesso ina una disfunzione almente al prevalere dello stato di ossidazione

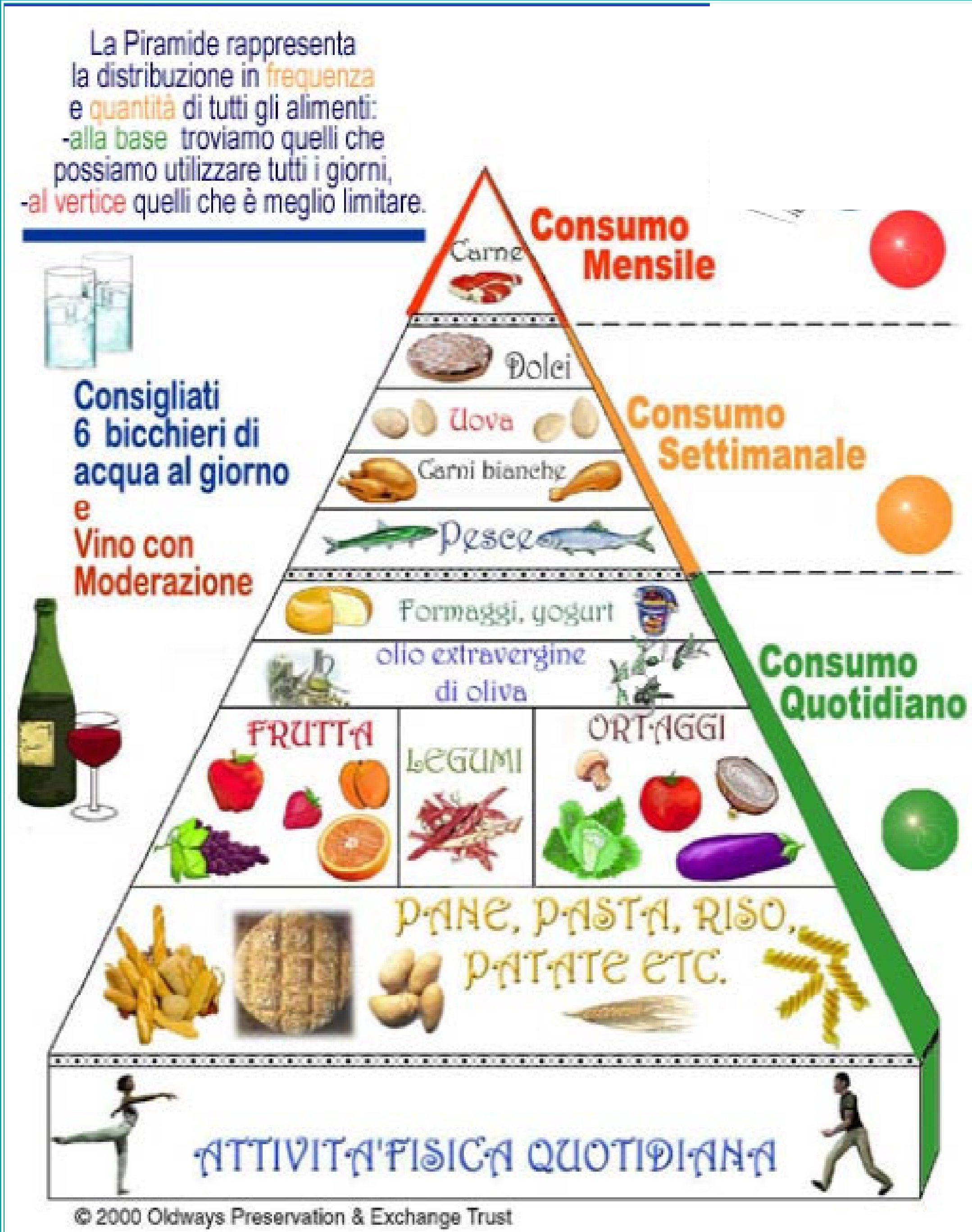
The Caloric Restriction

There is now evidence that indicates that caloric restriction acts by <u>decreasing oxidative stress</u> and damage and by increasing antioxidant defences and repair systems

Rao G et al. J Nutr 1990

Caloric restriction induces a hypometabolic state characterized by decreased reactive oxygen species and <u>decreased brain mithocondrial</u> O_2^- and reduced oxidative DNA damage in aged rats

Sanz A et al. J Bioenerg Biomembr 2005



- Il modello mediterraneo
- Esigenze nutritive
- Il latte
- I grassi
- La pasta
- Le fibre
- Le fibre vegetali
- La vitamina C
- Il sale (sodio)
- I salumi

… Da quando gli Dei insegnarono a coltivare i campi, i popoli della terra impararono che cereali e legumi, insieme ad altri semi o a verdure di vario tipo,talvolta con cibo di origine animale, offrivano perfette combinazioni alimentari…

Tortillas e fagioli (Americhe)

Semola e ceci (Cuscus, Nord-Africa)

Riso e soia (Oriente)

Riso e lenticchie/ Pasta e fagioli (Mediterraneo)

…La società agricola e la dieta cerealicola…

… Oggi…

Grande distribuzione…Globalizzazione…. Ritmi lavorativi…

carni / insaccati - grassi animali - margarine
farine raffinate - cibi precotti - fast-food

Stoccaggio/produzioni forzate
Gelificanti / addensanti
Aromatizzanti / conservanti / nitrati
Coloranti / emulsionanti

Alimentazione ipercalorica (+ 500Cal/die)

- Grassi saturi
- Proteine animali
- Zuccheri semplici

Malattie da civilizzazione

Obesità   Diabete   Ipertensione   Aterosclerosi   Stipsi
Osteoporosi   Infarto miocardico   Tumori intestinali…

…La Società industriale e la dieta carnea…

The Navajo Reservoir of North America

REVIEW ARTICLE

Drugs and Aging 2001:18(9) 685-716

Role of Free Radicals in the Neurodegenerative Diseases

Therapeutic Implications for Antioxidant treatment

Barry Halliwell

Department of Biochemistry, Faculty of Medicine, National University of Singapore

Alzheimer's Disease

The Brain is Highly Susceptible to Oxidative Damage:

- **Brain consumes 20% of the oxygen the body uses**
- **High Concentration of Fatty Acids - easily damaged**
- **Concentrates High Levels of Metals**
- **Contains Low Levels of Antioxidants**
- **Long-life Cells with Little Turnover**
- **Oxidative damage to mtDNA is several times higher in brain than in liver**

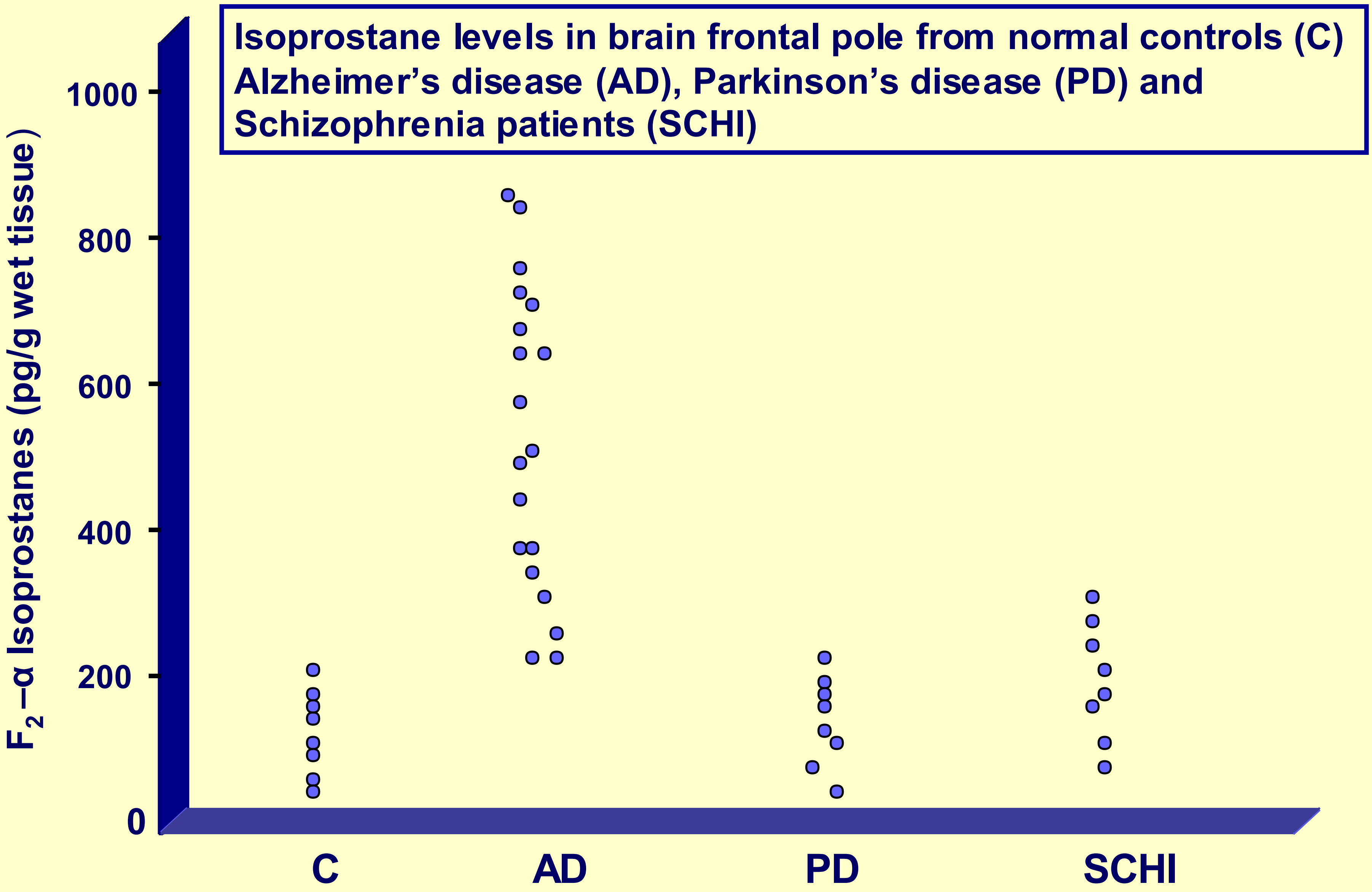
Barry Halliwell, Drugs and Aging 2001

The amyloid β-peptides are neurotoxic in cell culture, and many studies have implicated **reactive oxygen species** as major contributors to this toxicity

Yatin Sm et al. Neurobiol Aging 1999; Barkats M et al. J Neurochem 2000

Increased oxidative damage occurs in vivo in Alzheimer's disease, as determined by elevated DNA base and RNA oxidation products, protein carbonyls, HNE and other markers of lipid peroxidation in human brain

Practicò D et al Faseb J 1998;Markesbery WR et al. Brain Pathol 1999



Practicò D et al Faseb J 1998

Neuron, Vol. 39, 409–421, July 31, 2003, Copyright ©2003 by Cell Press

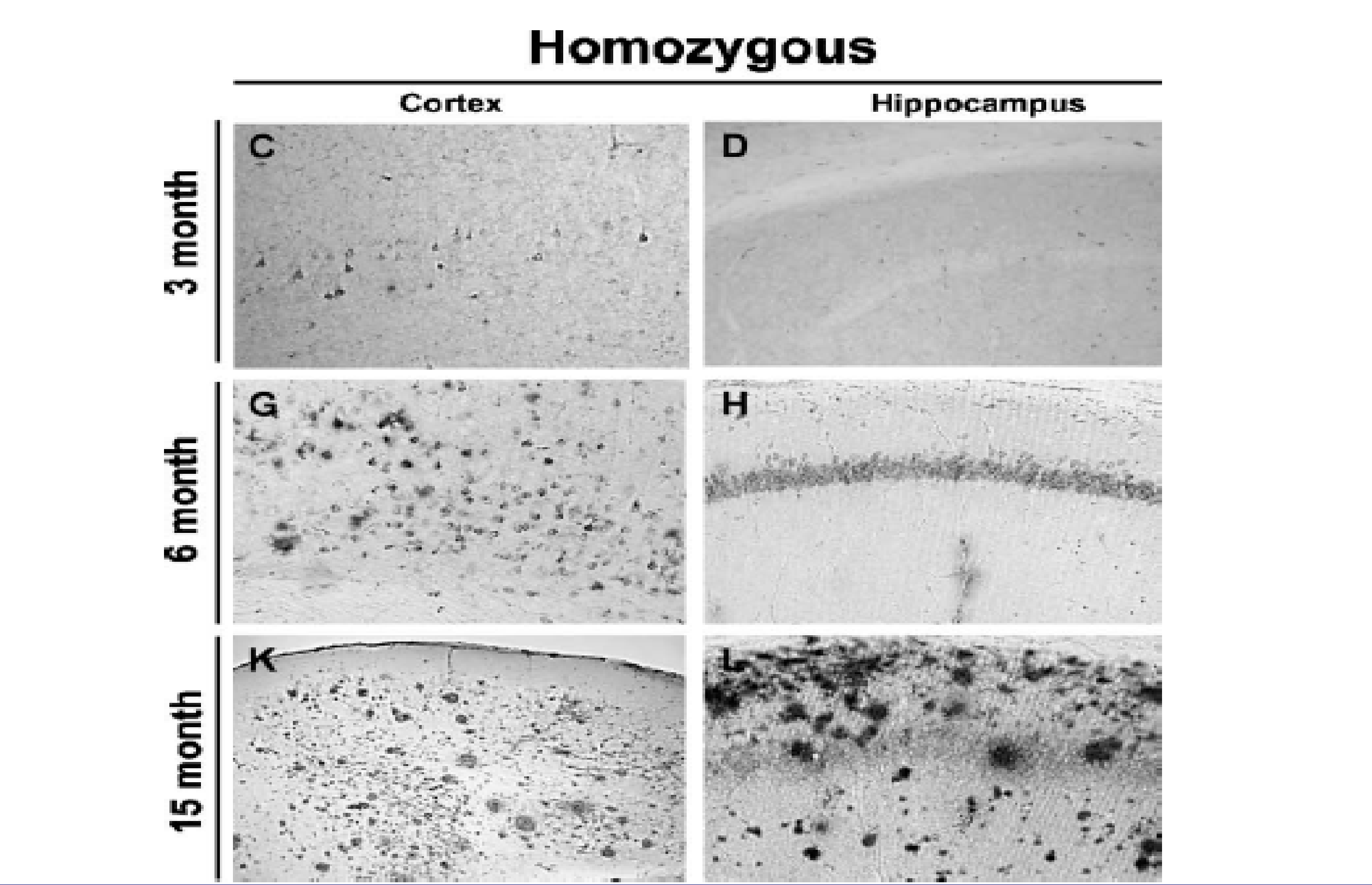
Triple-Transgenic Model of Alzheimer's Disease with Plaques and Tangles: Intracellular Aβ and Synaptic Dysfunction

Salvatore Oddo,[1] Antonella Caccamo,[1,5]
Jason D. Shepherd,[1,5] M. Paul Murphy,[3]
Todd E. Golde,[3] Rakez Kayed,[2]
Raju Metherate,[1] Mark P. Mattson,[4]
Yama Akbari,[1] and Frank M. LaFerla[1,*]

Three mutant genes:
-Presenilin-1 (PS1M146V)
-Amyloid Precursor Protein (APPSwe)
-and TauP301L.

The 3xTg-AD mice progressively develop Aβ and tau pathology, with a temporal- and regional-specific profile that closely mimics their development in the human AD brain.

Aβ-Pathology



Aβ deposition initiates in the cortex and progresses to the hippocampus. Coronal sections from 6- and 15-month-old homozygous mice were evaluated with an Aβ42-specific antibody. Extracellular Aβ deposits are evident by 6 months of age in the cortex, and by 16 months in the hippocampus.

Original magnifications, 10x.

Neuron, Vol. 39, 409–421, July 31, 2003, Copyright ©2003 by Cell Press

Triple-Transgenic Model of Alzheimer's Disease with Plaques and Tangles: Intracellular Aβ and Synaptic Dysfunction

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Raju Metherate,[1] Mark P. Mattson,[4]
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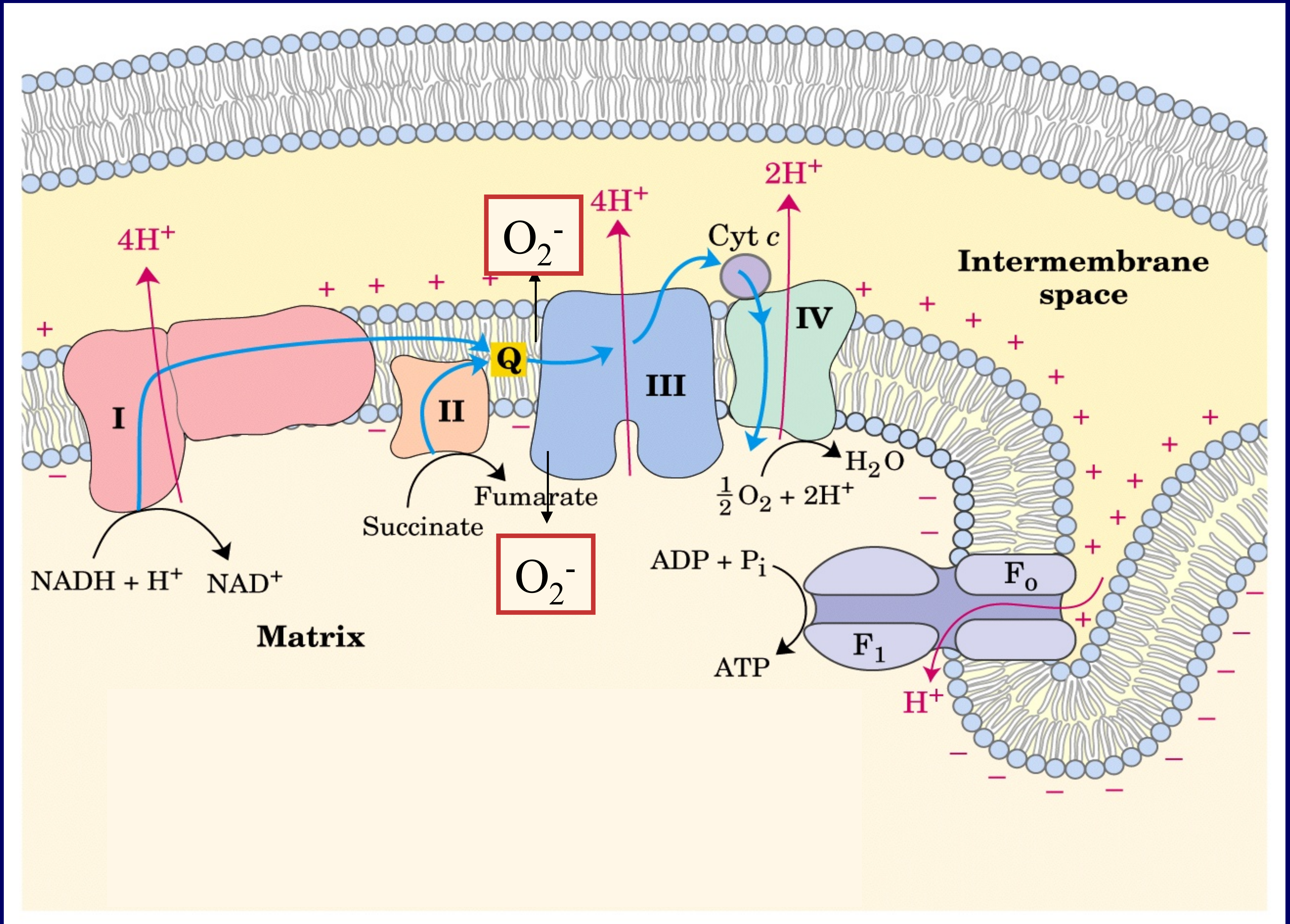
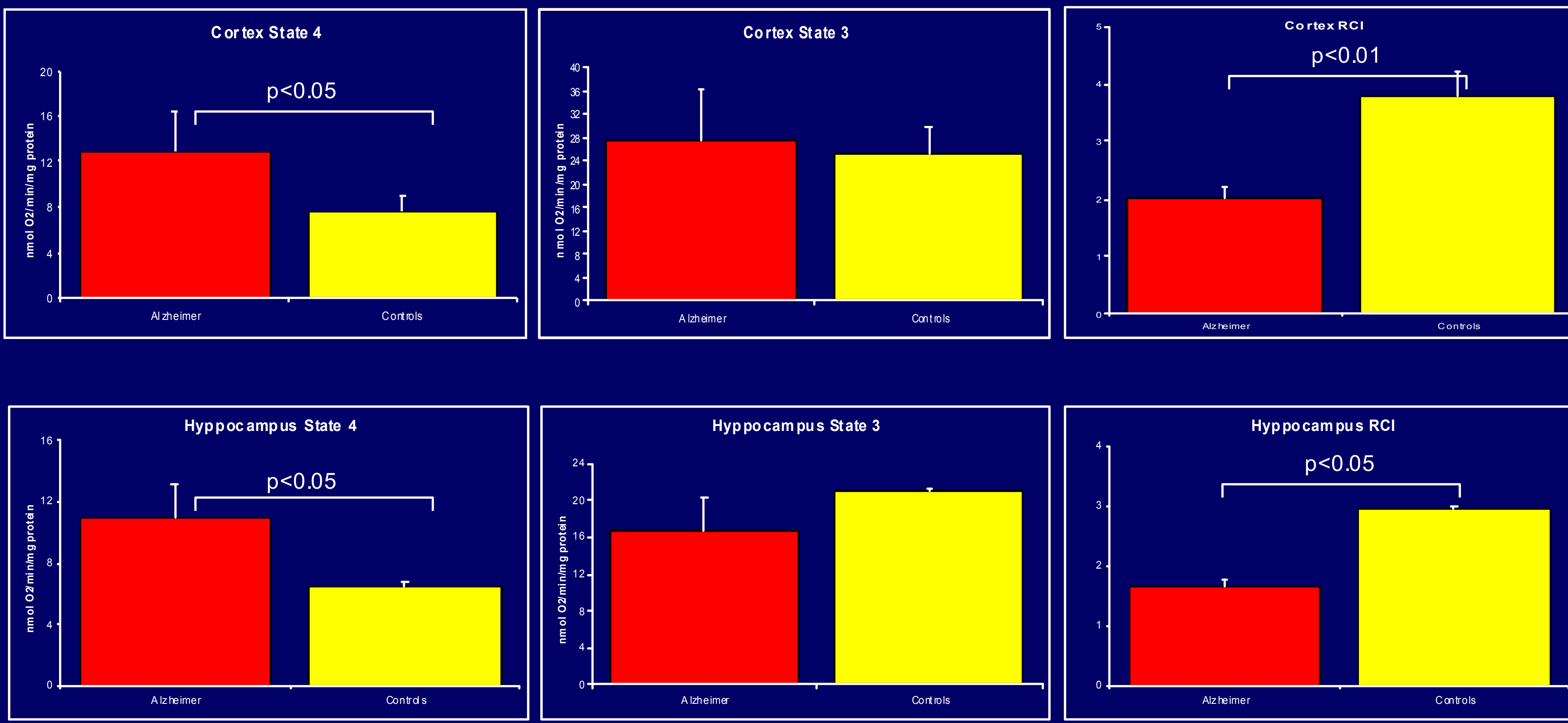
Aim of the study:

Mitochondrial Dysfunction in a Transgenic Model of Alzheimer's Disease

Oxygen reactions in respiration



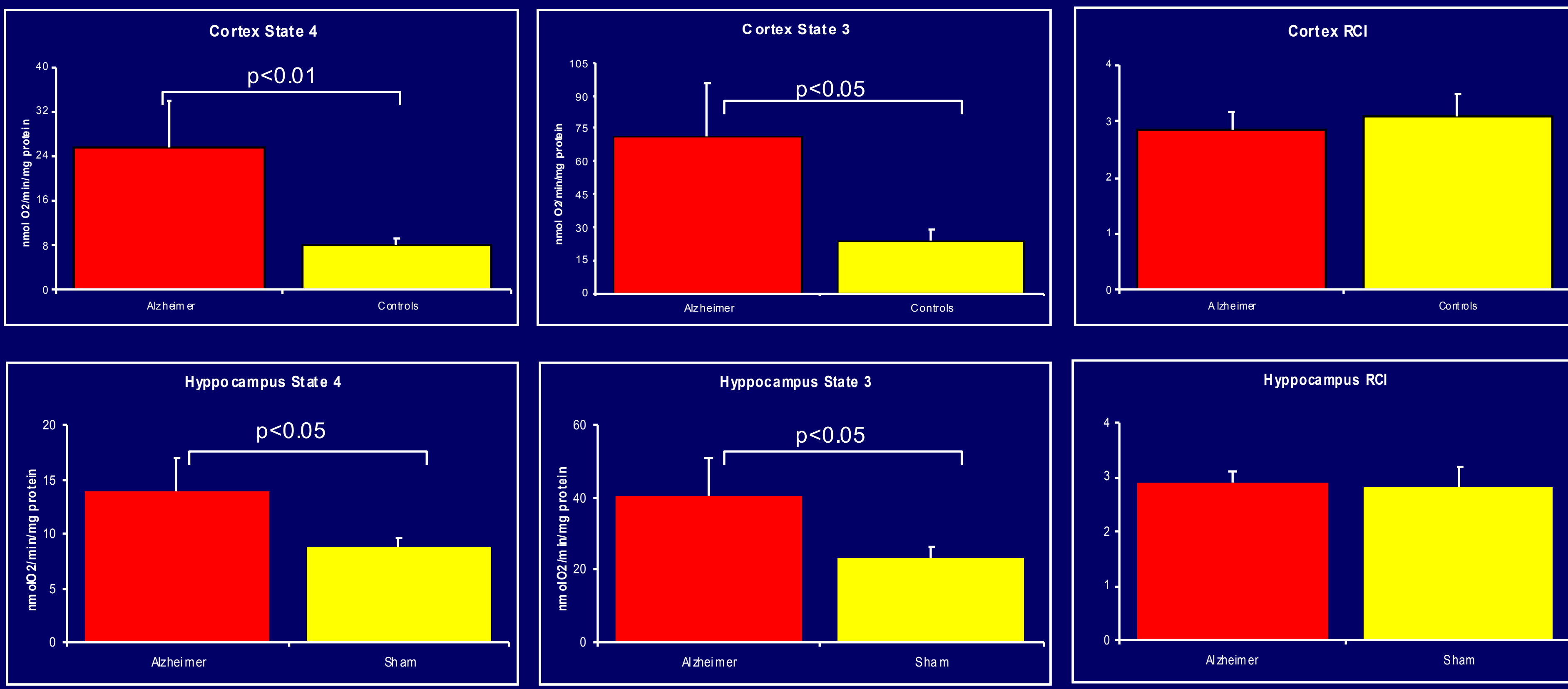
Complex I



Oxygen consumption and RCI at complex I in the respiratory chain

Vendemiale et al. In press

Complex II



Oxygen consumption and RCI at complex II in the respiratory chain

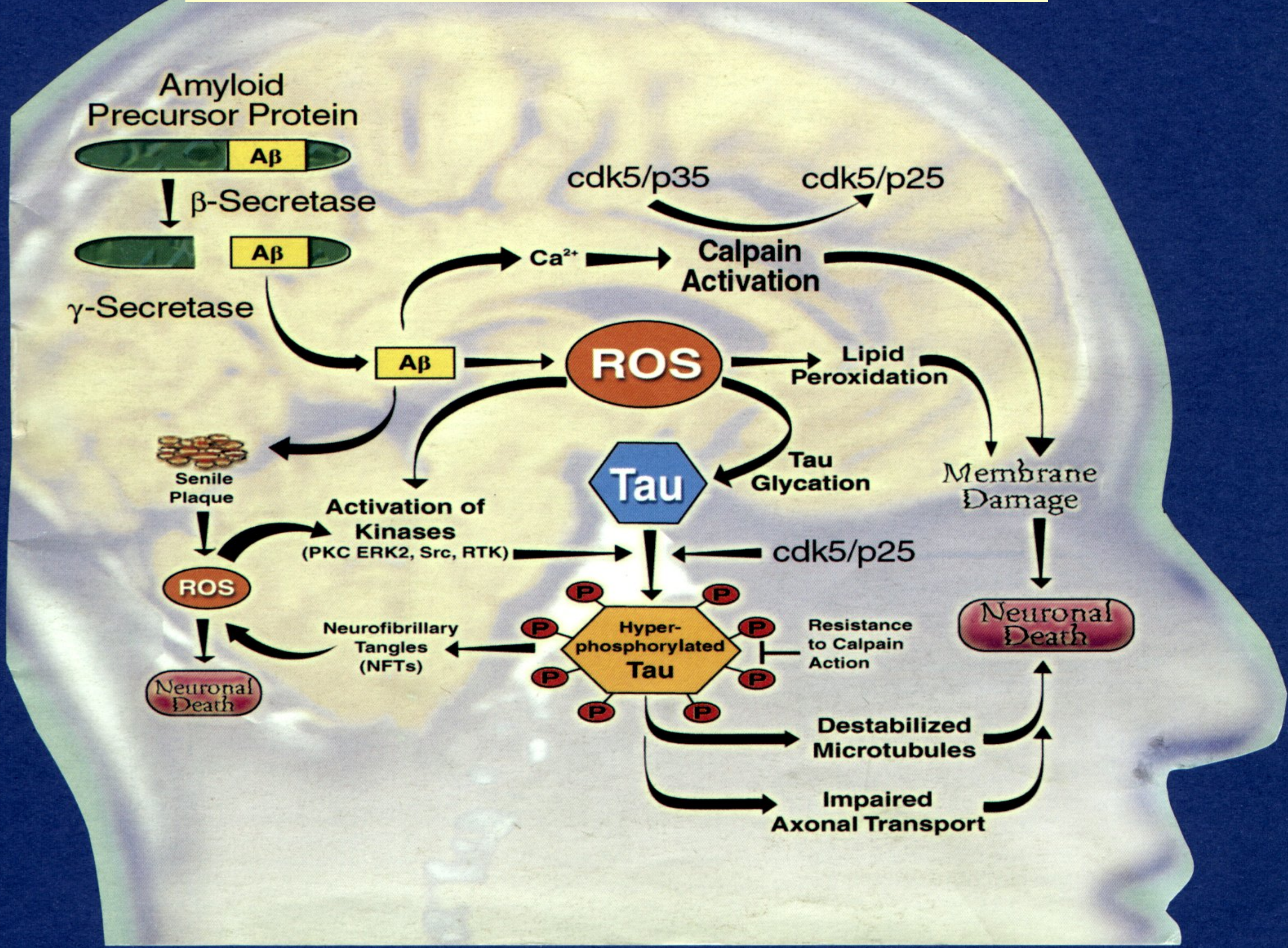
Vendemiale et al. in press

Conclusions

- **Brain from Alzheimer mice shows mitochondria bioenergetic impairment at Complex I and Complex II**
- **Complex II works, but in order to maintain the same membrane potential, the respiratory chain consumes more oxygen**

This is associated to an increased production of ROS

Ipotesi della cascata amiloidea



Journal of Gerontology: MEDICAL SCIENCES
2006, Vol. 61A, No. 3, 278–283

Lower Plasma Vitamin E Levels Are Associated With the Frailty Syndrome: The InCHIANTI Study

Alessandro Ble,[1] Antonio Cherubini,[2] Stefano Volpato,[3] Benedetta Bartali,[4] Jeremy D. Walston,[5] B. Gwen Windham,[1] Stefania Bandinelli,[6] Fulvio Lauretani,[7] Jack M. Guralnik,[8] and Luigi Ferrucci[1]

[1]Longitudinal Studies Section, Clinical Research Branch, National Institute on Aging, National Institutes of Health, Baltimore, Maryland.
[2]Institute of Gerontology and Geriatrics, University of Perugia, Italy.
[3]Department of Clinical and Experimental Medicine, Section of Internal Medicine and Geriatrics, University of Ferrara, Italy.
[4]Division of Nutritional Sciences, Cornell University, Ithaca, New York.
[5]Division of Geriatric Medicine and Gerontology, Johns Hopkins University, Baltimore, Maryland.
[6]Geriatric Rehabilitation Unit, Azienda Sanitaria di Firenze, Italy.
[7]Tuscany Region Health Agency, Firenze, Italy.
[8]Laboratory of Epidemiology, Demography and Biometry, National Institute on Aging, National Institutes of Health, Bethesda, Maryland.

Background. The primary biologic mechanism that causes frailty in older persons has never been adequately explained. According to recent views, oxidative stress may be the driving force of this condition. We tested the hypothesis that, independent of confounders, low plasma levels of vitamin E (α-tocopherol), the main fat-soluble human antioxidant, are associated with the frailty syndrome in older persons free from dementia and disability.

Methods. The study sample included 827 older (≥65 years) persons (women, 54%) who participated in a population-based epidemiological study. Frail participants were identified based on the presence of at least three of five of the following features: self-reported weight loss, low energy, slow gait speed, low grip strength, and low physical activity. Participants with none of these features were considered nonfrail, while participants with one or two were considered intermediate frail. Plasma vitamin E levels were determined using reverse-phase high-performance liquid chromatography. Measured confounders included lower extremity muscle strength, cognitive function, diseases, and factors related to vitamin E metabolism.

Results. Age- and gender-adjusted levels of vitamin E decreased gradually from the nonfrail to the frail group (p for trend = .015). In the logistic model adjusted for multiple potential confounders, participants in the highest vitamin E tertile were less likely to be frail than were participants in the lowest vitamin E tertile (odds ratio, 0.30; 95% confidence interval, 0.10–0.91).

Conclusions. Our findings show an association between low circulating levels of one of the most important components of the human antioxidant system and the presence of frailty.

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Archives of Biochemistry and Biophysics 458 (2007) 141–145

ABB

www.elsevier.com/locate/yabbi

Minireview

Carotenoids as protection against sarcopenia in older adults

Richard D. Semba *, Fulvio Lauretani, Luigi Ferrucci

Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA
Tuscany Regional Agency, Florence, Italy
Longitudinal Studies Section, Clinical Research Branch, National Institute on Aging, Baltimore, MD, USA

Received 4 August 2006, and in revised form 20 November 2006
Available online 6 December 2006

Abstract

Sarcopenia, or loss of muscle mass and strength, plays a major role in the disablement process in older adults and increases the risk of impaired physical performance, falls, physical disability, frailty, and death. Oxidative stress is a major mechanism implicated in the pathogenesis of sarcopenia; aging muscle shows increased oxidative damage to DNA, protein, and lipids. Carotenoids quench free radicals, reduce damage from reactive oxygen species, and appear to modulate redox-sensitive transcription factors such as NF-κB that are involved in the upregulation of IL-6 and other proinflammatory cytokines. Recent epidemiological studies in community-dwelling older adults show that low serum/plasma carotenoids are independently associated with low skeletal muscle strength and the development of walking disability. These observations are consistent with a growing number of studies showing that a diet with high intake of fruits and vegetables is associated with a reduced risk of inflammation, hypertension, diabetes, cardiovascular disease, and mortality.

Keywords: Aging; Carotene; Carotenoids; Cryptoxanthin; Inflammation; Lutein; Lycopene; Muscle; Sarcopenia; Zeaxanthin

Fragilità fisica

Positività di almeno 3 items tra i seguenti 5:

- Perdita di peso (≥ 4.5 Kg nell'ultimo anno)
- Affaticamento (riferito senso di fatica ≥ 3 gg/sett)
- Ridotta forza muscolare (Handgrip)
- Ridotta forza fisica (PASE)
- Ridotta velocità del cammino

Fried et al. 2001

SCOPO DELLO STUDIO

Valutare in una popolazione di anziani fragili l'eventuale presenza di marcatori biologici:

EQUILIBRIO REDOX:

- Glutatione ridotto (GSH) ed ossidato (GSSG)
- Malondialdeide (MDA), Idrossinonenale (HNE)

STATO INFIAMMATORIO:

- Tumor necrosis factor (TNF-α)

MATERIALI E METODI

Popolazione studiata: Pazienti ricoverati nell'UOC di Medicina Interna dell'IRCCS "Casa Sollievo della Sofferenza" (1/03 -31/05/2007)

Età > 65 anni

Criteri di esclusione: Alterazioni acute o croniche in grado di non rendere valutabili gli items della scala di Fried o di rendere inaffidabile il dosaggio dei marcatori di stress ossidativo

Consenso informato alla partecipazione allo studio

60 pazienti

DISEGNO DELLO STUDIO

SOGGETTI STUDIATI

N=60

CRITERI DI FRIED 3/5

FRAGILI

N=41

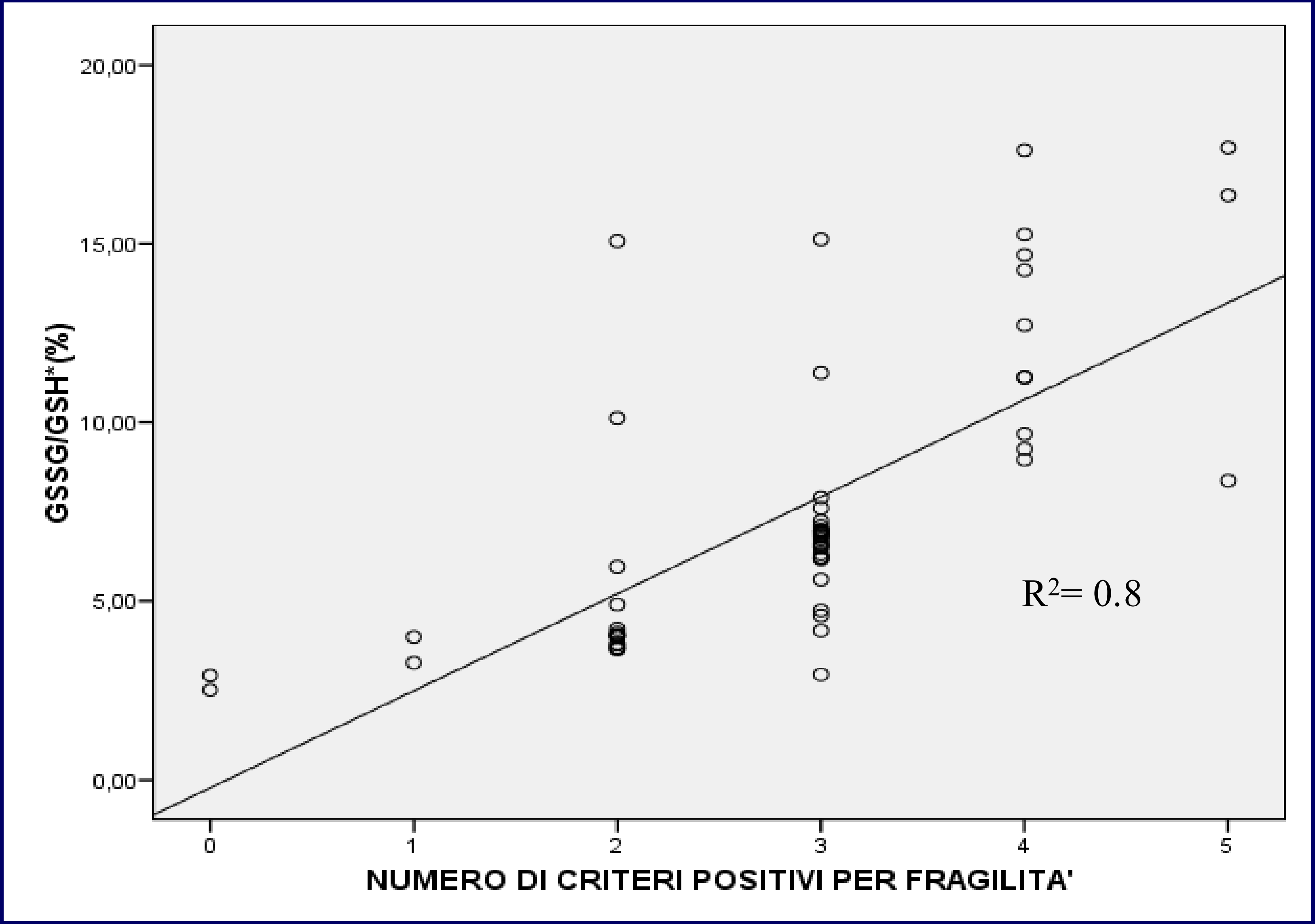
NON FRAGILI

N=19

Variabili biochimiche
(confronto fragili vs non fragili)

Variabile	Fragili	Non fragili	Signif.
GSSG (μM)	61.1±31.9	35.6±11.1	$p<0.001$
GSH (μM)	701.7±198.8	799.6±134.9	$p<0.001$
GSSG/GSH%	4.8±2.9	8.7±3.8	$p<0.001$
MDA (aUF/mgr prot)	36.4±33.7	9.6±2.3	$p<0.001$
HNE(aUF/gr prot)	39.2±3.0	11.2±3.8	$p<0.001$
TNF α	2.2±1.2	0.3±0.2	$p<0.001$

CORRELAZIONE TRA NUMERO DEGLI ITEMS POSITIVI PER FRAGILITA' E STATO REDOX



CONCLUSIONI

Marcatori di stress ossidativo e di flogosi risultano significativamente aumentati nei soggetti anziani fragili rispetto ai non fragili

⇓

Possibili determinanti biologici della condizione che identifica la vulnerabilita' dell'anziano

A Ginkgo Biloba Extract Prevents Mitochondrial Aging By Protecting Against Oxidative Stress

Sastre J et al. Free Radic Biol Med 1998

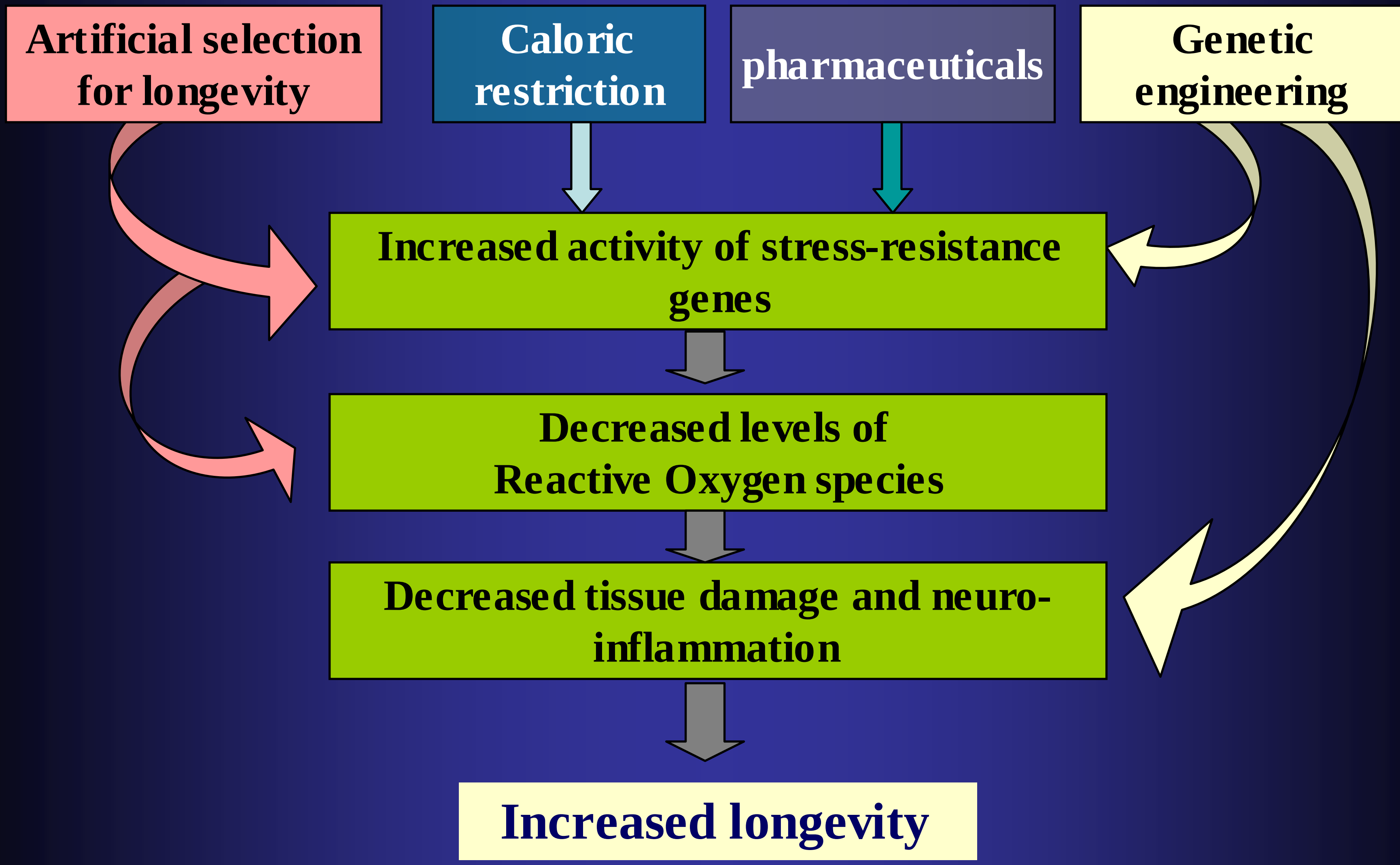
Vitamin E at High Doses Improves Survival, Neurological Performance, And Brain Mitochondrial Function In Aging Mice

Navarro A et al. Am J Physiol 2005

Effect of Antioxidant Diets on Mitochondrial Gene Expression in Rat Brain During Aging

Nicoletti VG et al. Neurochem Res 2005

Oxidative stress-related pathways



..People don't die from age: they die from disease..

Lotta Granholm – Center on Aging
Medical University of South Carolina

Malattia di Alzheimer

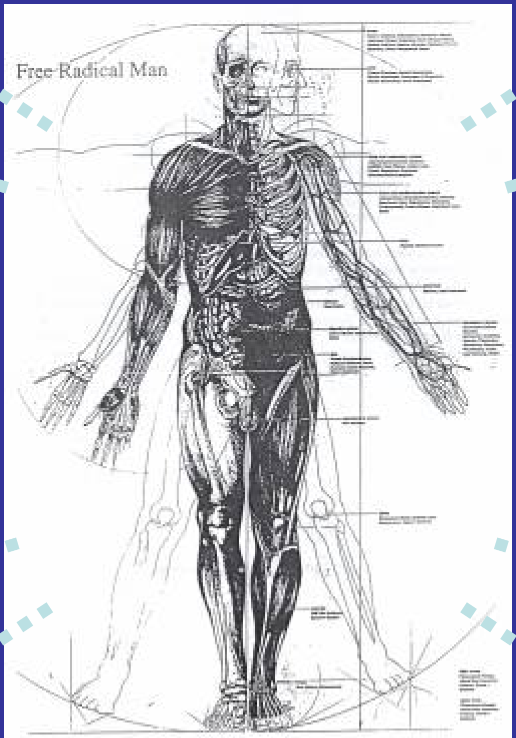
Stroke

Aterosclerosi

Pancreatite

Infarto del miocardio

Obesità



INVECCHIAMENTO

Malattia di Parkinson

Cataratta

Artrite reumatoide

Malattia di Chron

Diabete mellito

Cancro

"The free radical man"

George Perry and Mark A. Smith,Case Western Reserve University Cleveland, Ohio