60° CONGRESSO NAZIONALE

NAPOLI

25-28 Novembre 2015

Infiammazione cronica: possibile ostacolo all'invecchiamento di successo

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Cellular senescence and the senescent secretory phenotype: therapeutic opportunities

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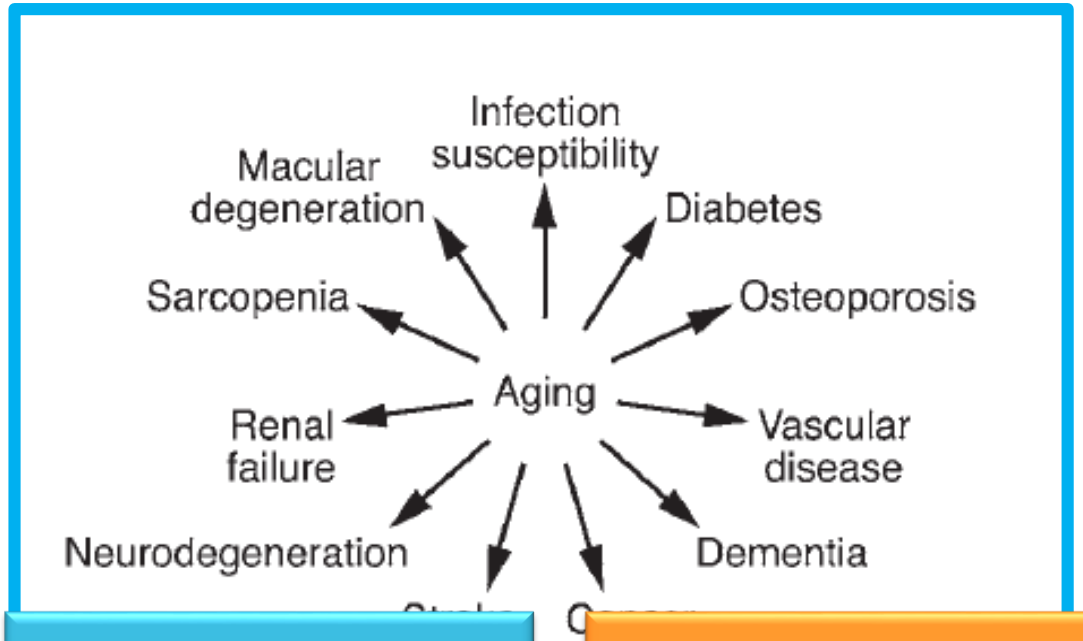

Immunosenescenza

Infiammazione cronica

ness, and frailty.

ANNALS of THE NEW YORK ACADEMY OF SCIENCES

Inflamm-aging: An Evolutionary Perspective on Immunosenescence

CLAUDIO FRANCESCHI[1,2,*], MASSIMILIANO BONAFÈ[1], SILVANA VALENSIN[1], FABIOLA OLIVIERI[2], MARIA DE LUCA[4], ENZO OTTAVIANI[3] and GIOVANNA DE BENEDICTIS[4]

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Issue

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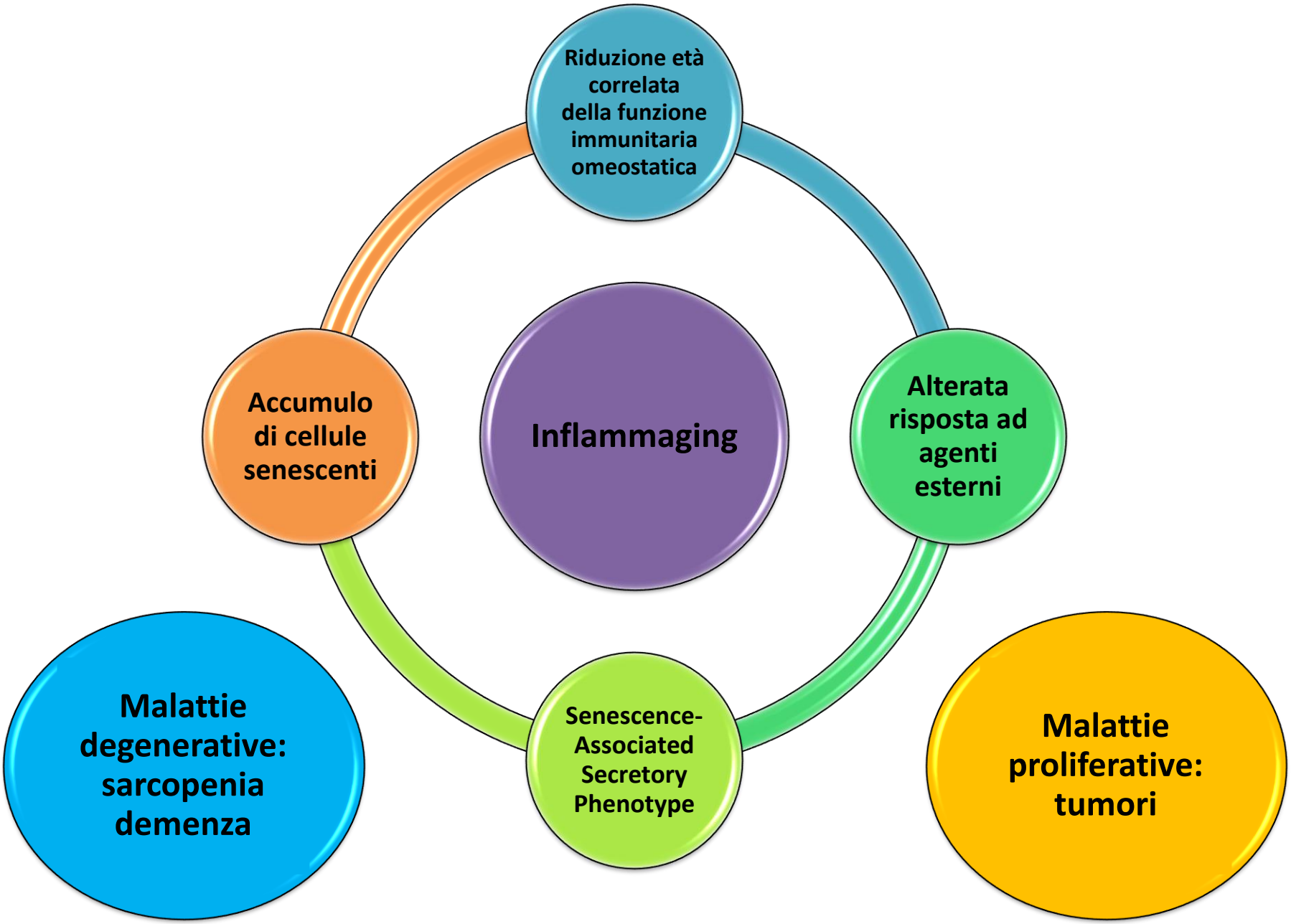
Inflammaging: chronic, low-level state of systemic and sterile (in the absence of overt infection) inflammation, which represent a pervasive feature of human aging and probably one of its major causes

Inflammaging

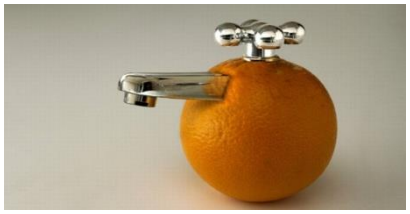
- Infiltrazione di cellule immunitarie che degradano il tessuto e rilasciano frammenti tossici o reattivi
- Le citochine determinano cambiamenti fenotipici INDIPENDENTI DAL SISTEMA IMMUNITARIO.
  - Es. IL 6 e IL 8
    - Attivano l'angiogenesi
    - Alterano la comunicazione tra cellule
    - Bloccano la funzione macrofagica
    - Inducono la risposta innata
    - Promuovono la migrazione e l'invasione del tessuto da parte di cellule epiteliali ed endoteliali


Riduzione età correlata della funzione immunitaria omeostatica
Accumulo di cellule senescenti
Inflammaging
Alterata risposta ad agenti esterni
Senescence-Associated Secretory Phenotype
Malattie degenerative: sarcopenia demenza
Malattie proliferative: tumori

Senescence-Associated Secretory Phenotype SASP

Previous studies have shown that the culture medium of senescent cells is enriched with secreted proteins. When cells become senescent, they often display a **senescence-associated secretory phenotype** consisting of cytokines, growth factors, and proteases, which collectively have been termed the “senescence-associated secretory phenotype” (SASP) by the Campisi group. Kuilman and Peeper termed the same phenomenon as the “senescence messaging secretome”.

The contribution of senescence might seem to be passive, but the recentdiscovery of SASP strongly suggests that senescence might have a more **active** and pathologically diverse role to play



Premature lung aging and cellular senescence in the pathogenesis of idiopathic pulmonary fibrosis and COPD/emphysema

MARCO CHILOSI, ANGELO CARLONI, ANDREA ROSSI, and VENERINO POLETTI

VERONA, TERNI; AND FORLÌ, ITALY

(Translational Research 2013;162:156–173)

Premature aging and epithelial stem cell exhaustion.
Mechanical stress can explain the location of early damage and remodeling in IPF.
Cellular senescence and molecular mechanisms in lung remodeling and bronchiolar proliferative lesions in IPF.
Abnormal cell signaling and tissue remodeling in IPF.
Immunosenescence, inflammaging, and acute IPF exacerbations.
Accordingly, systemic immune-related defects have been described recently in IPF patients with poor prognosis and rapid progression that are likely related to immunosenescence and inflammaging, including abnormalities in innate immunity Toll-like receptor sensors as well as the marked downmodulation of CD28 on circulating CD4 T cells.165-167 Toll-like receptor signaling is involved in the functional decline in an ability to respond to new pathogens during aging,168 and CD28 is a critical costimulatory molecule on T cells. CD28 downmodulation is considered a reliable marker of CD8 T cell replicative senescence and age-related decline of immunocompetence

Table 1. Comparing Senescence-Associated Secretory Phenotype and Chronic Obstructive Pulmonary Disease–Associated Secretory Phenotype

SASP Factors	Secretory Profile for Human Fibroblasts and Prostrate Epithelial Senescent Cells (Reference Number) (44, 49)	Secretory Profile for Human COPD Lung (Reference Number)
Interleukins		(75, 76, 132)
IL-6	↑*	↑
IL-1α, -1β	↑	↑
IL-13	↑	↑
Chemokines (CXCL, CCL)		(77, 78)
IL-8	↑	↑
GRO-α,-β,-γ	↑	↑
MCP-2	↑	↑
MIP-1a, -3a	↑	↑
Other inflammatory factors		(83, 133)
GM-CSF		↑
MIF		↑
Growth factors and regulators		
EGF	↑	↑ (134)
bFGF	↑	↑ (115, 135)
VEGF	↑	↑ (79)
Angiogenin	↑	↑ (79)
IGFBP-3	↑	↑ (58)
Proteases and regulators		
MMP-1, -3, -10, -12, -13, -14		↑ (90–93)
PAI-1, PAI-2, uPAR		↑ (137, 138)
Cathepsin B	↑	↑ (139)
Soluble or shed receptors or ligands		
ICAM-1, -3		↑ (105, 140)
OPG	↑	↑ (141)
TRAIL-R3, sTNFRI, Fas sTNFRII	↑	↑ (142)
uPAR	↑ (98)	↑ (98, 138)
EGF-R	↑	↑ (80)
Nonprotein factors		
PGE2	↑	↑ (110, 112)
Nitric oxide	↑	↑ (118, 124, 125)
Reactive oxygen species	↑	↑ (143)
Extracellular matrix proteins		(115, 144)
Fibronectin		↑
Collagens		↑
Laminin		↑

Interleuchine

Chemochine

Altri fatt. infiammatori

Fattori di crescita e regolatori

Proteasi e regolatori

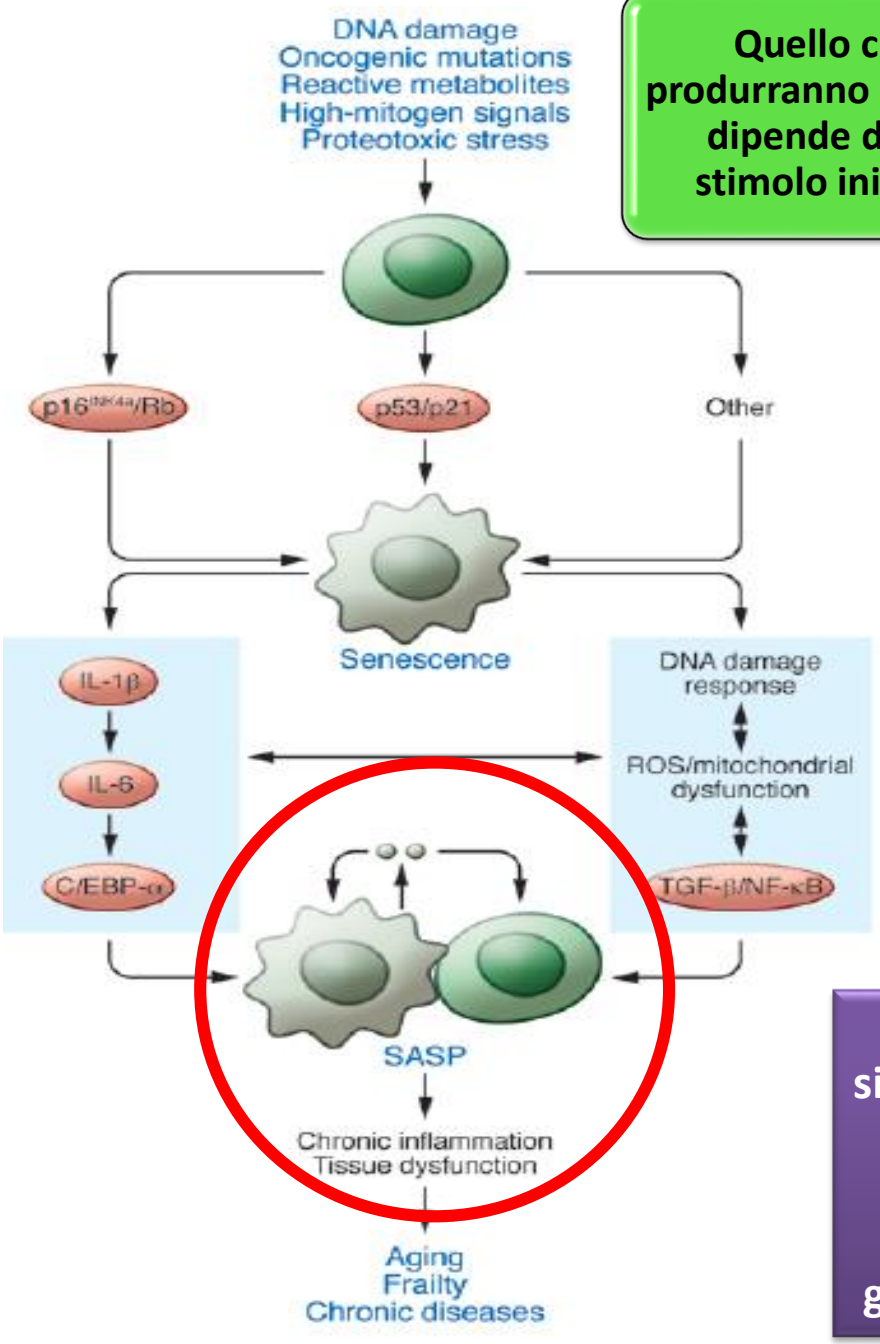
Recettori e ligandi solubili o non solubili

Fattori non proteici

Proteine della matrice extracellulare

Definition of abbreviations: bFGF, basic fibroblast growth factor; COPD, chronic obstructive pulmonary disease; EGF, endothelial growth factor; EGF-R, endothelial growth factor receptor; GM-CSF, granulocyte macrophage colony stimulating factor; GRO, growth-related oncogene; ICAM, intercellular adhesion molecule; IGFBP, insulin-like growth factor–binding protein; MCP, monocyte chemoattractant protein; MIF, macrophage migration inhibitory factor; MIP, macrophage inflammatory protein; MMP, matrix metalloproteinase; OPG, osteoprotegerin; PAI, plasminogen activator inhibitor; PGE2, prostaglandin E2; SASP, senescence-associated secretory phenotype; sTNFRI, soluble tumor necrosis factor receptor; TRAIL, tumor necrosis factor–related apoptosis-inducing ligand; uPAR, urokinase-type plasminogen activator receptor; VEGF, vascular endothelial growth factor.
*Arrows indicate increase in the levels of the secreted molecule.

Figure 1. Many roads lead to senescence, but not all cause the senescence-associated secretory phenotype (SASP) response. HRAS, transfection of GTPase HRas; OIPS, oncogene-induced premature senescence; PTEN, phosphatase and tensin homolog; SIPS, stress-induced premature senescence.



Quello che produrranno le SASP dipende dallo stimolo iniziale

Se le cellule senescenti vengono rimosse, il danno tissutale si blocca

Ad un certo punto il sistema immunitario, che è senescente anche lui (sistema innato e i suoi macrofagi), non è più in grado di eliminare le SASP

Cellular senescence and the senescent secretory phenotype: therapeutic opportunities

Tamara Tchkonia,[1] Yi Zhu,[1] Jan van Deursen,[1] Judith Campisi,[2] and James L. Kirkland[1]

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- Intervenire nei pathway che causano l'arresto della crescita associato alla senescenza.
  - Strada difficilmente percorribile, perché provoca tumori. Tuttavia la restrizione calorica
    - Riduce il turnover dei progenitori delle cell. senescenti
    - Riduce il danno metabolico
    - Riduce altri processi di danno cellulare
- Eliminare le cellule senescenti:
  - Anticorpi che riconoscano epitopi per eliminare le cell. Senescenti
  - Piccole molecole che uccidono selettivamente solo quel tipo di cellule: Glucocorticoidi (solo le SASP)
- "Pilotare" la produzione da parte delle cell. SASP

Nutritional stimuli

↓

Epigenetic changes
Gut microbiota - Brain
Immune system
INFLAMMATION

↓

Long term effects
on health and longevity

NU-AGE and Inflammaging

BASIC HYPOTHESIS & RATIONALE

Appropriate WHOLE DIET (an *ad hoc* fortified "Mediterranean diet") can decrease the level of the chronic, sub-clinical, low grade inflammatory process characteristic of old age we have proposed to call INFLAMMAGING (Franceschi et al., 2000)

NU-AGE will built
a mathematical model of inflammaging and Mediterranean diet
capable of integrating all risk factors, processes, mechanisms (pathways), modulators (specific nutrients)

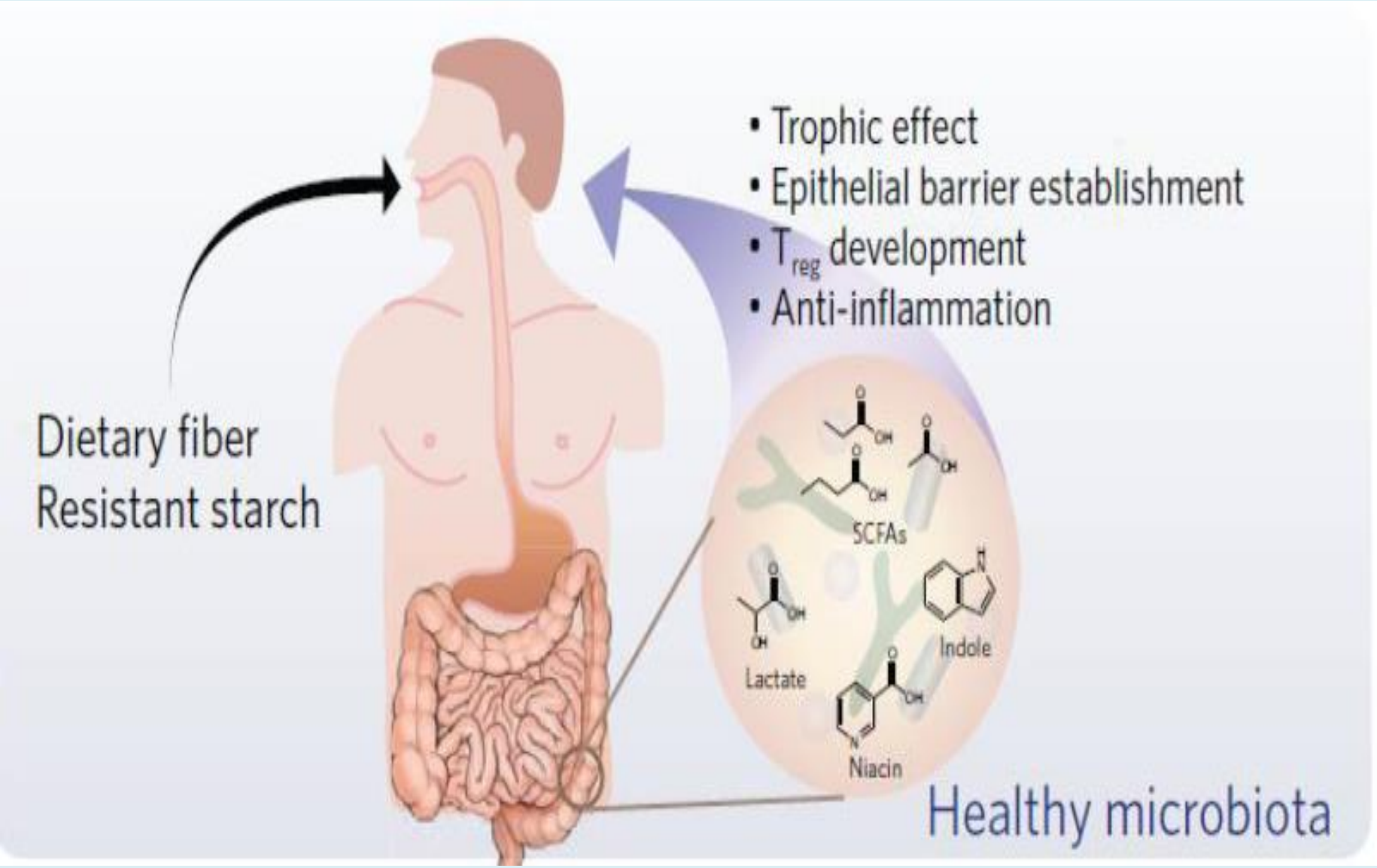
Appropriate DIET
for the elderly

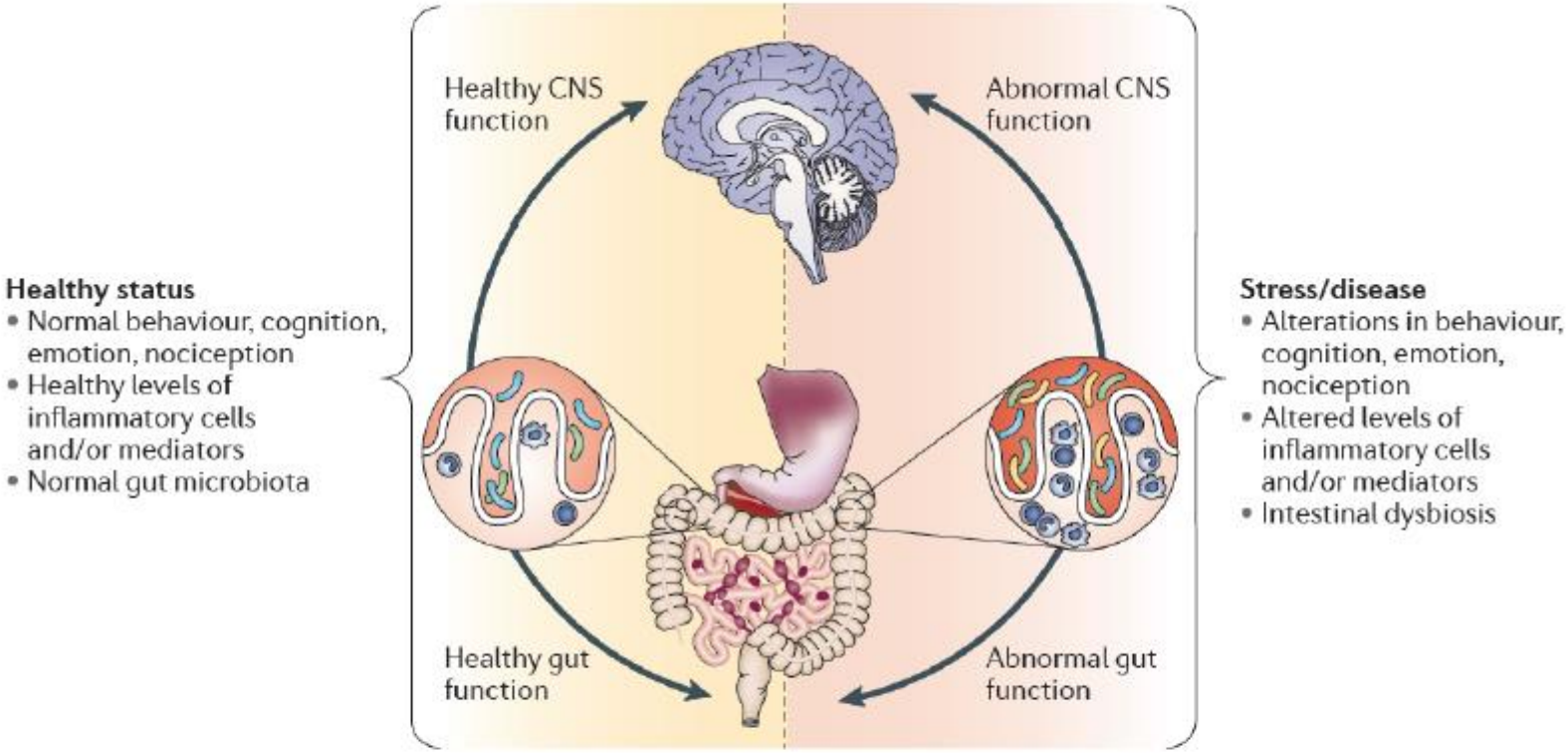
+

Gut microbiota Imm Syst
Metabolome Epigenome

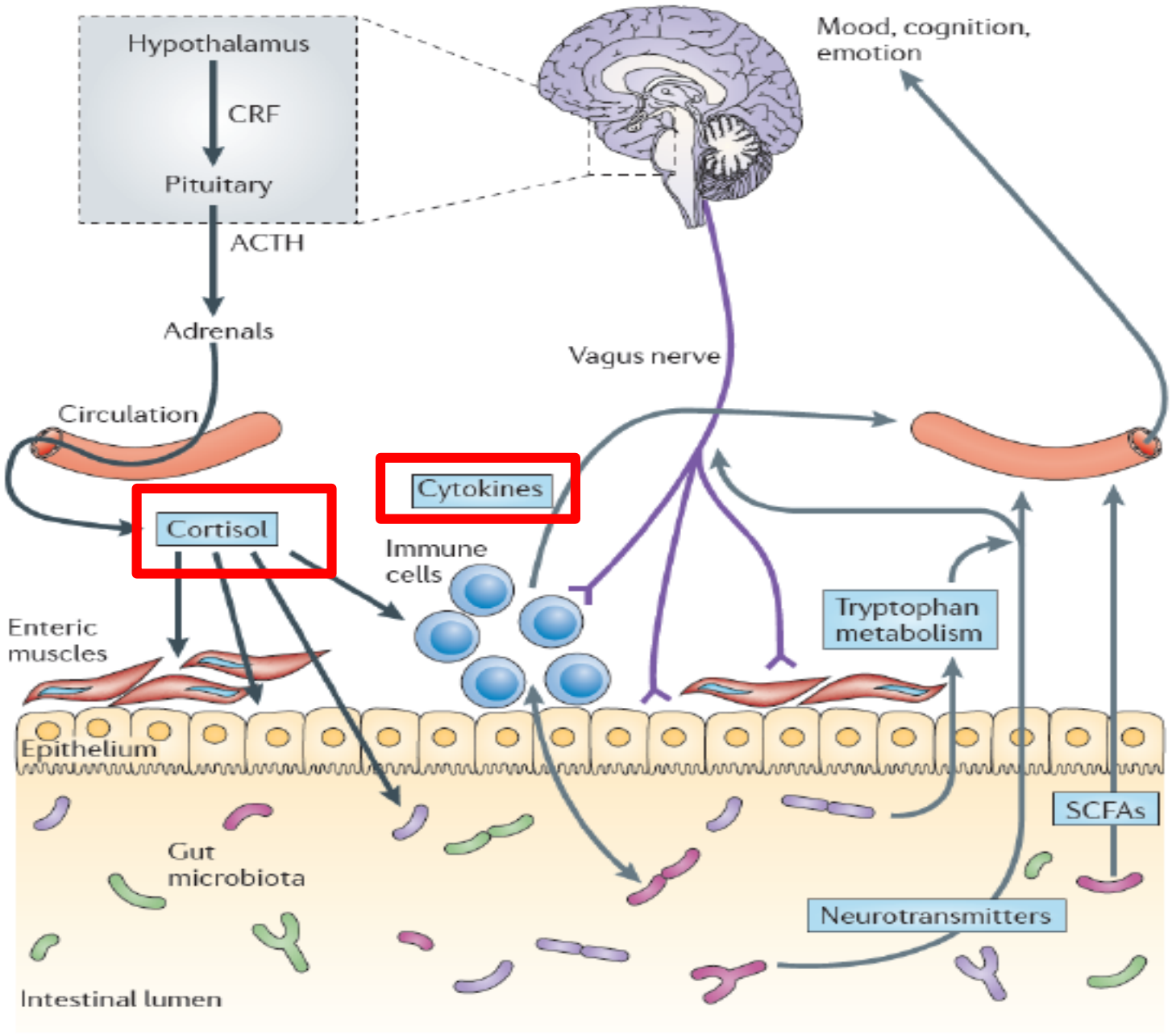
−

↓ inflammaging
↓ age-related diseases


• Trophic effect
• Epithelial barrier establishment
• T_{reg} development
• Anti-inflammation
Dietary fiber
Resistant starch
SCFAs
Lactate
Indole
Niacin
Healthy microbiota



The gut-brain axis


Hypothalamus
CRF
Pituitary
ACTH
Adrenals
Circulation
Cortisol
Cytokines
Immune cells
Enteric muscles
Epithelium
Gut microbiota
Intestinal lumen
Vagus nerve
Mood, cognition, emotion
Tryptophan metabolism
SCFAs
Neurotransmitters

- The concept of "**METAFLAMMATION**" (metabolic inflammation) has been proposed, to point out **the systemic and pervasive state of inflammation observed in response to excess of nutrients** and energy.
- **Nutrient excess can engage the classical pathogen sensing or immune-response pathways**, such as TLRs present in most cells of the body and **recognized as antigens & inflammatory stimuli**
- **High levels of free fatty acids and glucose** induce a stress in the pancreatic islets and in adipose tissue, liver and muscle inducing the local release of cytokines, chemokines and adipokines

Cura della patologia cronica → **NON FERMO** L'INVECCHIAMENTO → Es. Se si elimina il K come causa di morte, la lifespam aumenta del 3-4%

Identifico e modifico il **MECCANISMO** che porta alla patologia cronica → **FERMO** L'INVECCHIAMENTO → Es. La restrizione calorica, che agisce sui meccanismi, aumenta la lifespam

RENDO L'INVECCHIAMENTO UN FATTORE MODIFICABILE

9 Diet Tips to Help You Fight Inflammation

July 17, 2015 / By Heart & Vascular Team

By Katherine Patton, MEd, RD, CSSD, LD

http://health.clevelandclinic.org/2015/07/9-diet-tips-to-help-you-fight-inflammation/?utm_campaign=inmotion+enews&utm_medium=email&utm_source=im1510&utm_content=diet+inflammation

1. Scegli amidi derivati da grano integrale, mangia frutta con la buccia e molta verdura. Questi cibi hanno una più alta concentrazione di nutrienti e contengono moltissime vitamine e minerali necessari per mantenere e migliorare la salute.
2. Consuma una varietà di frutta, verdura e semi di vari colori, cercando di variare di settimana in settimana, per ottenere il massimo della quota nutrienti con il minimo sforzo.
3. Limita amidi raffinati (bianchi) e zuccheri aggiunti (bianco o di canna, bibite gassate, bibite energetiche). Questi cibi meno ricchi di nutrienti promuovono un pattern pro-infiammatorio come aumento di peso, glicemia elevata, aumento delle concentrazioni plasmatiche di lipidi.
4. Choose skinless poultry, fish, eggs, legumes and fat-free Greek yogurt. These are quality sources of protein, as well as additional sources of calcium, vitamin D, probiotics and unsaturated fat.
5. Limit high-fat red meat such as prime rib, bacon and sausage, as well as processed meats like bologna, salami and hot dogs. These are higher in saturated fat, which if consumed in excess will increase inflammation.
6. Scegli grassi mono-insaturi e Omega-3 , che si pensa neutralizzino l'infiammazione. I primi si trovano nell'olio di oliva, nell'avocado e nelle nocciole. Il consumo di questi cibi riduce il rischio di patologie cardiache e di cancro, associati ad alti livelli di inflammaging.
7. Gli acidi grassi Omega-3 si trovano nel tonno e nel salmone, nelle noci e nei semi di lino. Omega-3 è un acido grasso essenziale che noi non riusciamo a produrre, quindi lo dobbiamo ottenere dalla dieta o dai supplementi. Questi acidi grassi riducono l'infiammazione associata all'esercizio.
8. Limita gli acidi grassi saturi (latte intero, burro, formaggi, carne rossa, pelle del pollo, ecc.). L'eccesso accentua l'infiammazione.
9. Evita I grassi trans (cibi confezionati e ricchi di insaporenti, snak al cioccolato o allo yogurt, ecc.) Non c'è un livello di sicurezza. Riducono il colesterolo buono, aumentano, riciclano e rimettono in circolo il colesterolo LDL, considerato pro-infiammatorio.

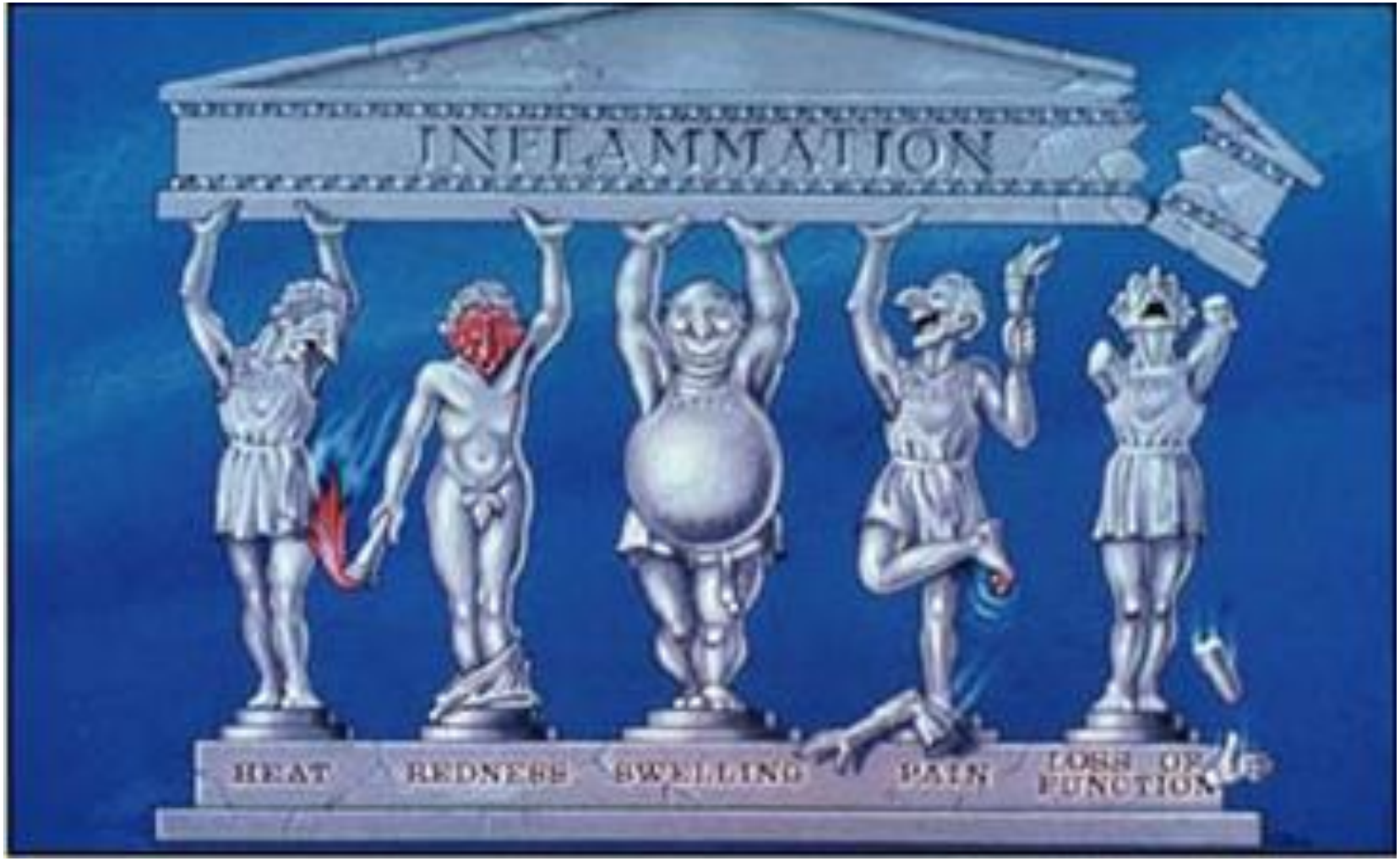
ESSAY OF THE MONTH

Aging Process Speeded By Chronic Inflammation

By Beth Balen on March 31, 2014 · 1 Comment

Researchers continue to look for therapies or diets that could prevent chronic diseases through reducing excessive inflammation processes. In the meantime there are some **tried and true** suggestions for improving overall health that may also reduce chronic inflammation.

- **Control weight**: In addition to controlling weight, it is important to pay attention to where the body is putting on fat. Accumulating fat in the waist area can indicate chronic inflammation.
- **Control stress and get enough sleep**: Stress has been found to be related to the accumulation of belly fat. Stress hormones bind to receptors on fat cells, encouraging storage of fat and increasing the number of fat cells. These cells produce more chemicals that increase inflammation.
- **Exercise**: But in moderation. Research suggests that extensive workouts can actually increase inflammation. 60 minutes of activity at one time gives the health benefits needed without risking increased inflammation.
- **Diet**: Follow a Mediterranean-style diet that includes plenty of fruits, nuts, vegetables, olive oil, and fish to protect the heart and lower the levels of chemicals that encourage inflammation. Include antioxidant-rich foods, green tea, and Omega-3 fatty acids.
- **Floss and brush daily**: There is a well-established connection between heart disease and gum disease.
- **Probiotics**: UCLA School of Medicine researchers report that intestinal inflammation could be related to white blood cell damage in other parts of the body, resulting in a whole body inflammatory response.



GRAZIE!