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03 · 04 · 05
APRILE 2025

Inflammaging accelerato

Pietro Gareri, MD, PhD
Responsabile CDCD Catanzaro Lido
ASP Catanzaro

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Key points

- Cos'è l'inflammaging
- Legame con le malattie croniche dell'invecchiamento
- Invecchiamento accelerato…le possibili conseguenze nell'ottica delle malattie neurodegenerative

- 'Inflammaging' refers to the chronic, low-grade inflammation that characterizes aging

- Inflammaging is macrophage centered, involves several tissues and organs, including the gut microbiota, and is characterized by a complex balance between pro- and anti-inflammatory responses

- The major source of inflammatory stimuli is represented by endogenous/self, misplaced, or altered molecules resulting from damaged and/or dead cells and organelles, recognized by receptors of the innate immune system

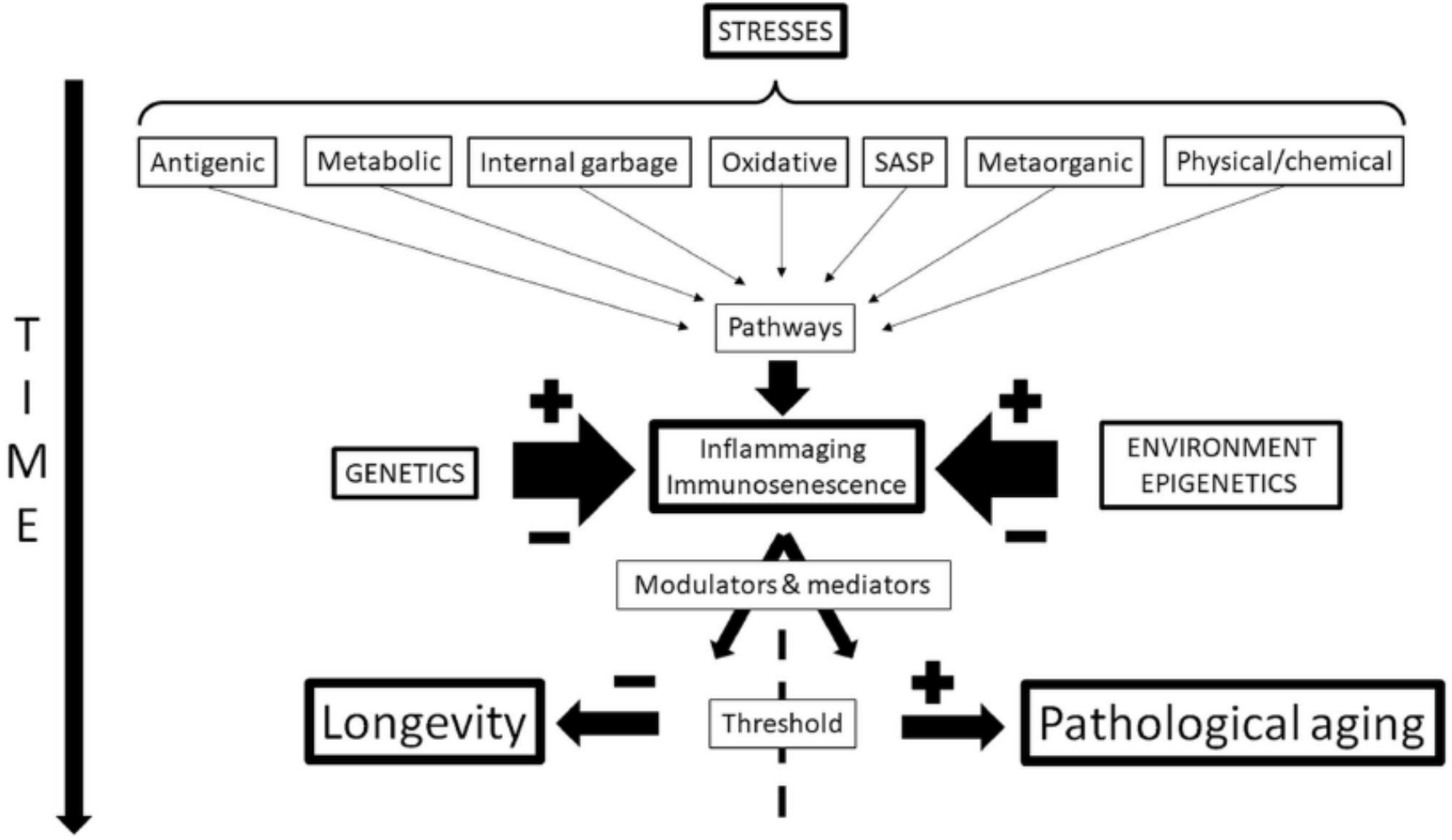
- While their production is physiological and increases with age, their disposal by the proteasome via autophagy and/or mitophagy progressively declines. This 'autoreactive/autoimmune' process fuels the onset or progression of chronic diseases that can accelerate and propagate the aging process locally and systemically

Trends Endocrinol Metab; 2017 Mar;28(3):199-212.
doi: 10.1016/j.tem.2016.09.005. Epub 2016 Oct 24.

Inflammaging and 'Garb-aging'

Claudio Franceschi, Paolo Garagnani, Giovanni Vitale, Miriam Capri, Stefano Salvioli

Inflammaging can be considered a major target for antiaging strategies


STRESSES
Antigenic
Metabolic
Internal garbage
Oxidative
SASP
Metaorganic
Physical/chemical
Pathways
TIME
GENETICS
Inflammaging
Immunosenescence
ENVIRONMENT
EPIGENETICS
Modulators & mediators
Longevity
Threshold
Pathological aging

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International Journal of
Molecular Sciences

MDPI

Review

Inflammaging and Immunosenescence as Part of Skin Aging—A Narrative Review

Justyna Pająk, Danuta Nowicka * and Jacek C. Szepietowski

Mol. Sci. **2023**, *24*, 7784. https://doi.org/10.3390/ijms24097784

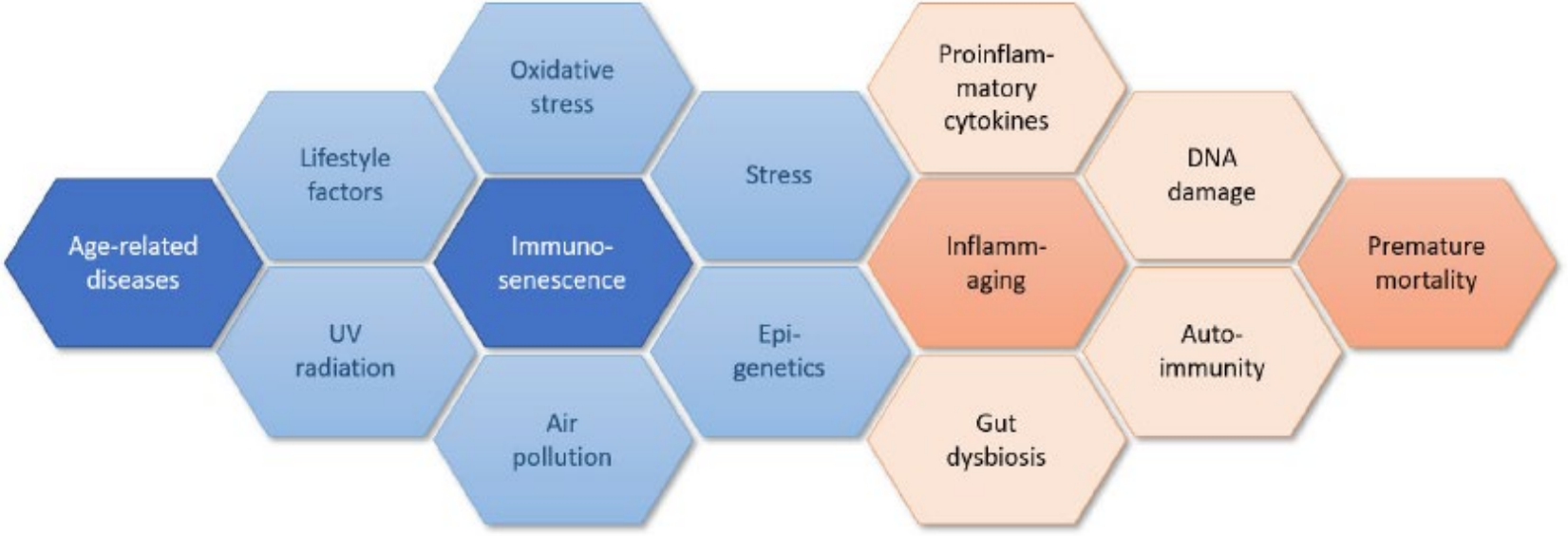


Figure 1. Factors contributing to immunosenescence and inflammaging.

2-023-01502-8

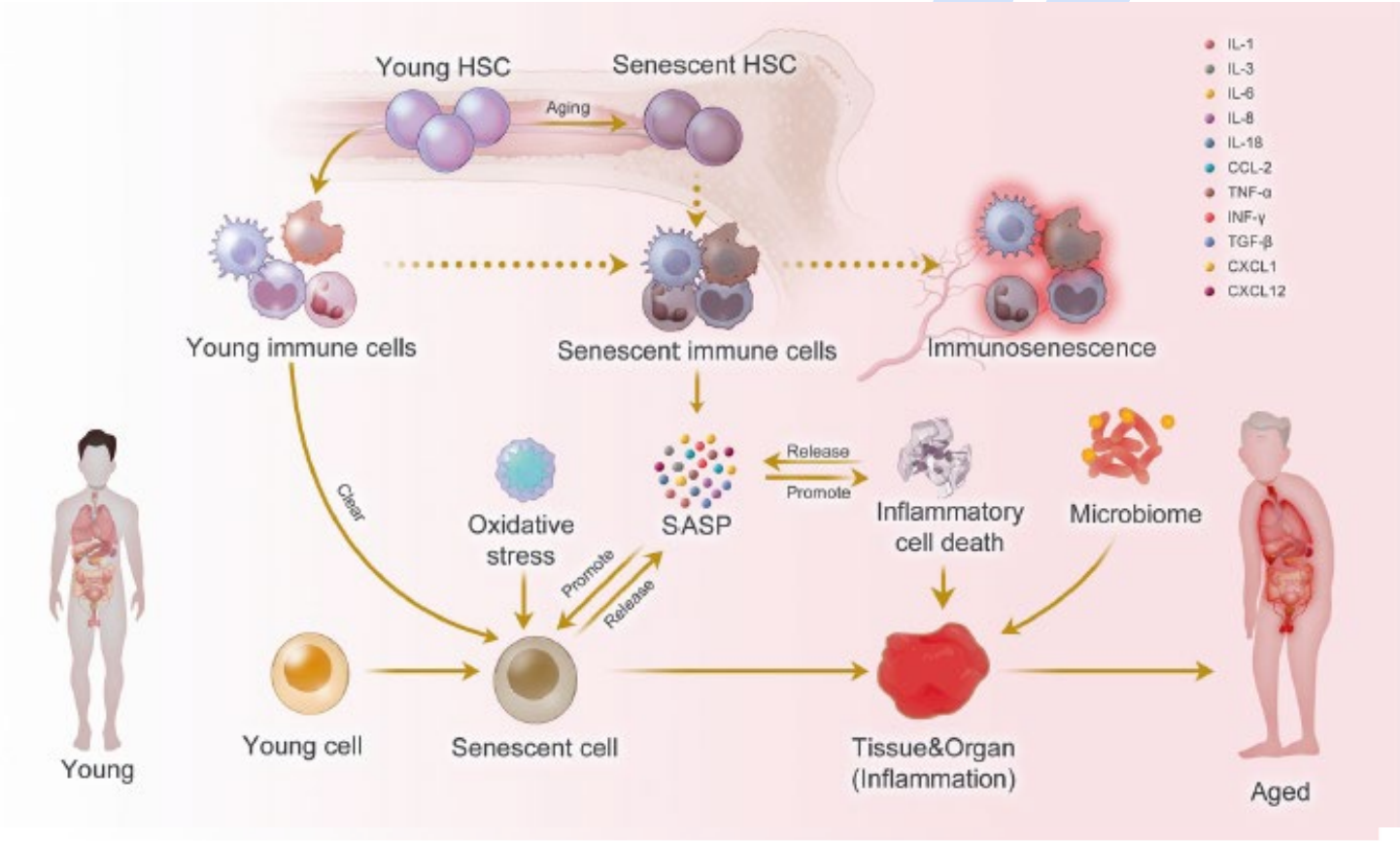


Fig. 1 Inflammaging at the molecular, cellular, and organ levels. During the aging process, almost all cells in the body undergo senescence, a state characterized by a dysfunctional state and senescence-associated secretory phenotype (SASP). While immune cells play a crucial role in recognizing and eliminating these senescent cells, they are also affected by SASP, leading to a phenomenon called immunosenescence. Immunosenescence can impair the immunity to respond to infections and diseases, making the organism more vulnerable to illnesses. Moreover, the accumulation of senescent cells can trigger inflammation in organs, leading to organ damage and an increased risk of age-related diseases. This process is exacerbated by positive feedback loops that drive the accumulation of inflammation and organ damage, leading to further inflammation and an even higher risk of aging-related diseases

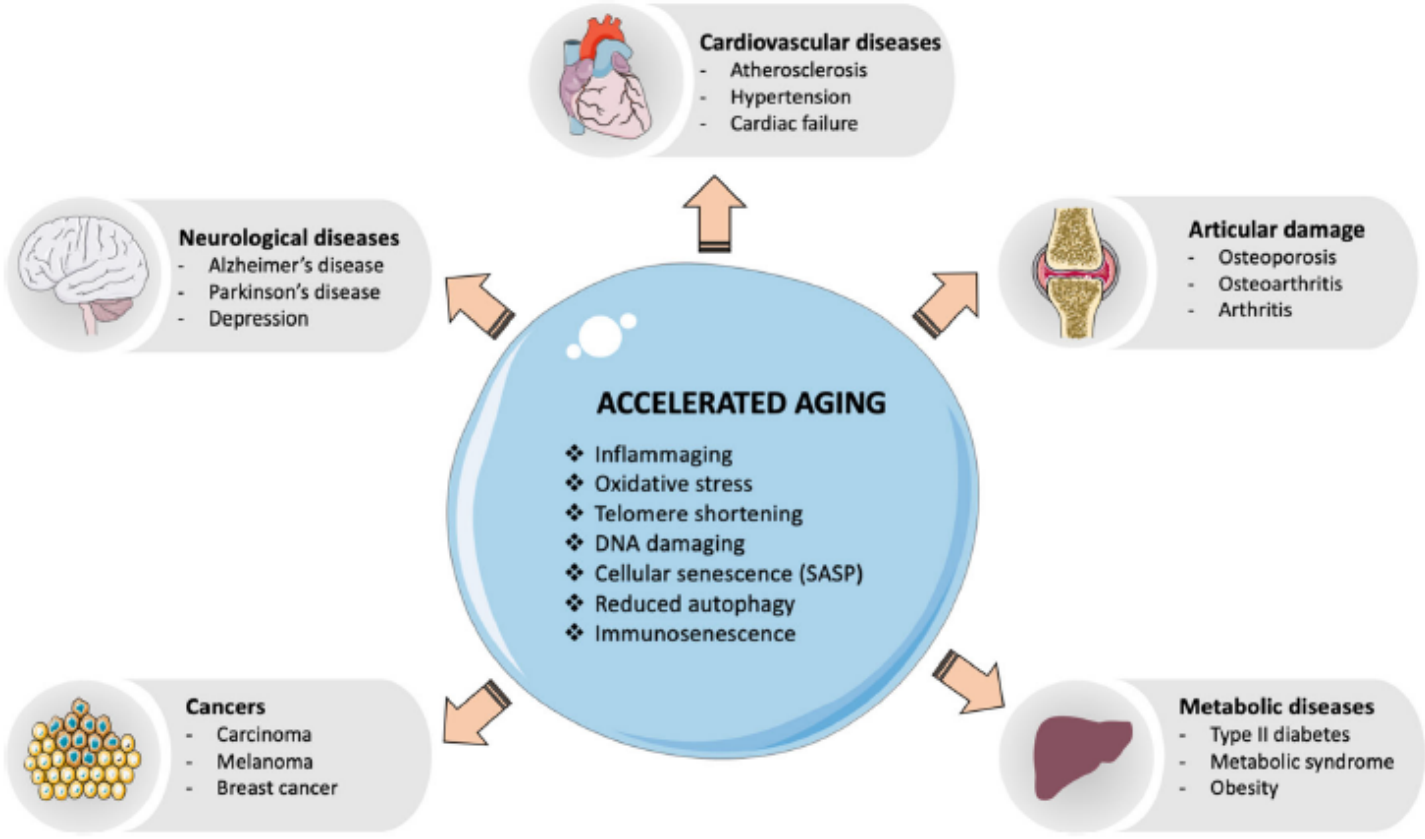
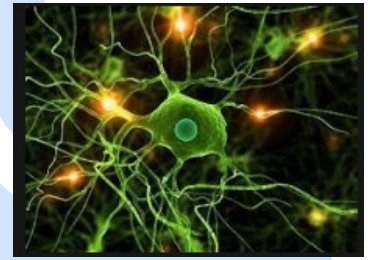


Fig. 1 Multiple mechanisms of accelerated aging are similarly found in age-related diseases. Abbreviations: CMV, cytomegalovirus; SASP, senescence-associated secretory phenotype

Dai neuroni all'UNITA' NEUROVASCOLARE



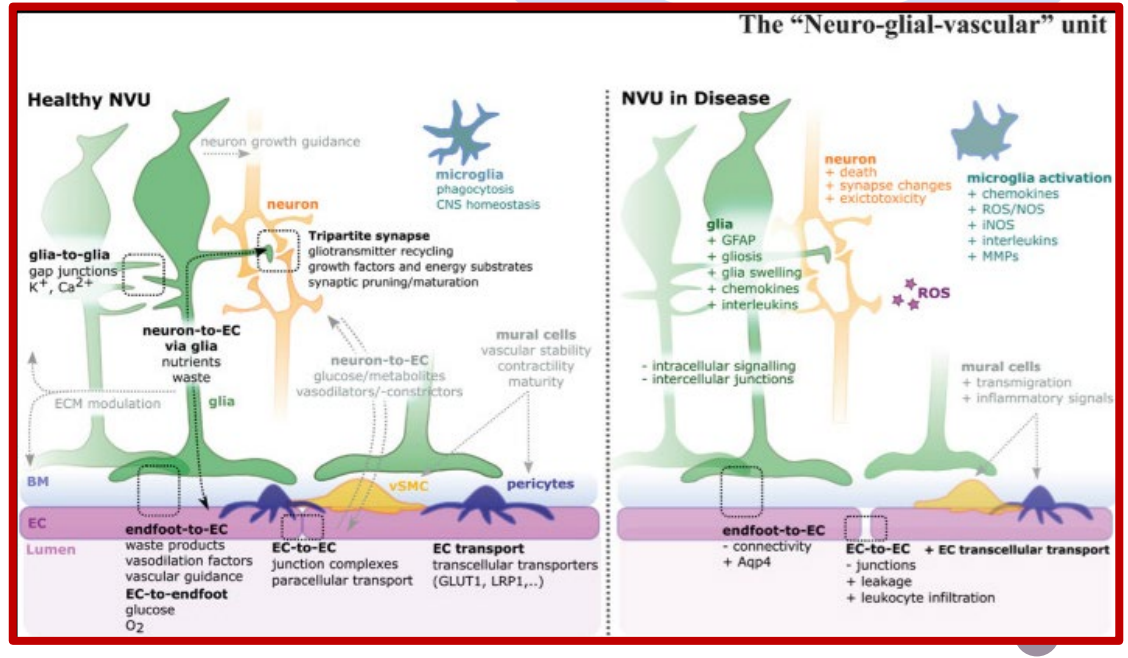
The "Neuro-Glial-Vascular" Unit: The Role of Glia in Neurovascular Unit Formation and Dysfunction

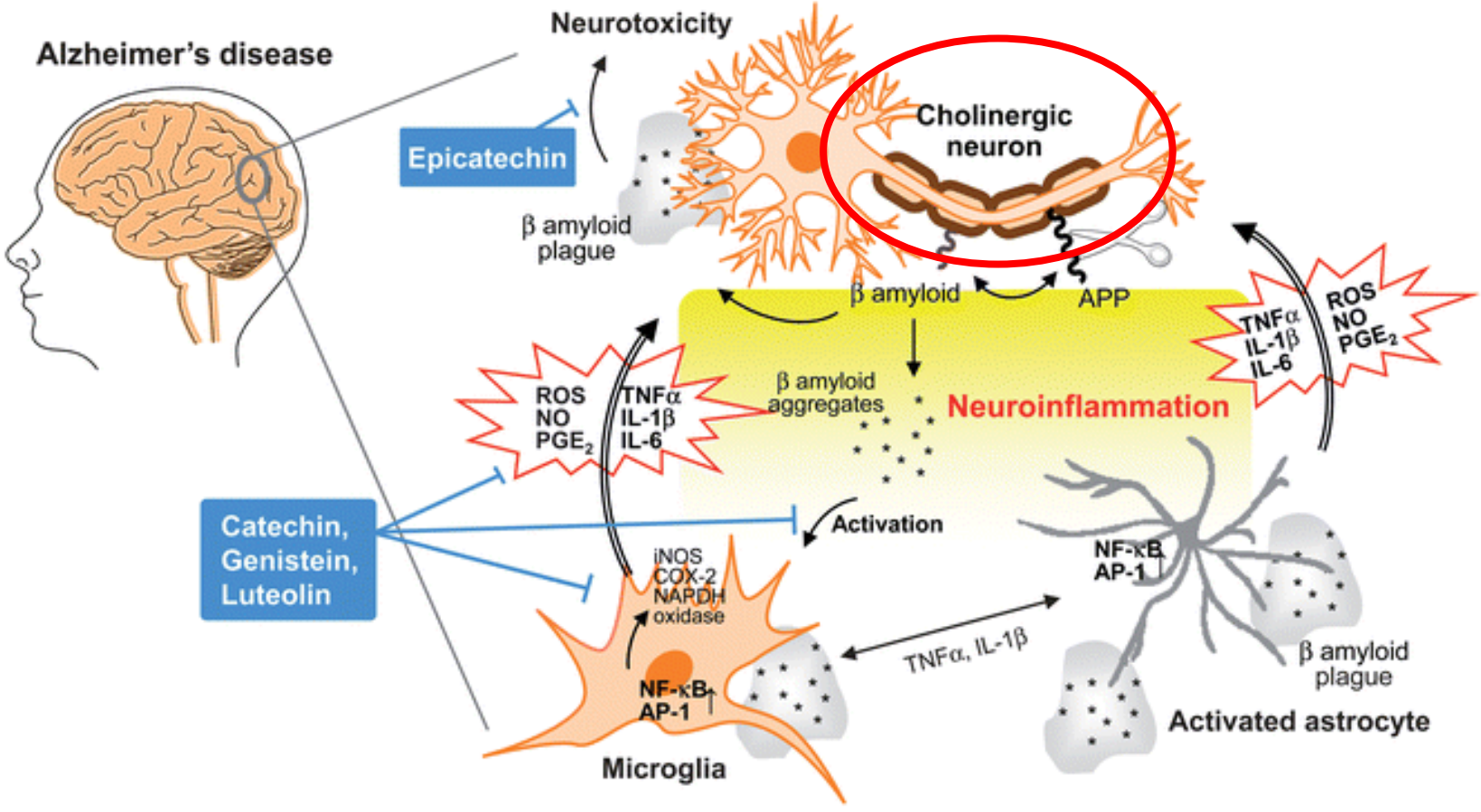
Elisabeth C Kugler [1], John Greenwood [1], Ryan B MacDonald [1]

Affiliations + expand

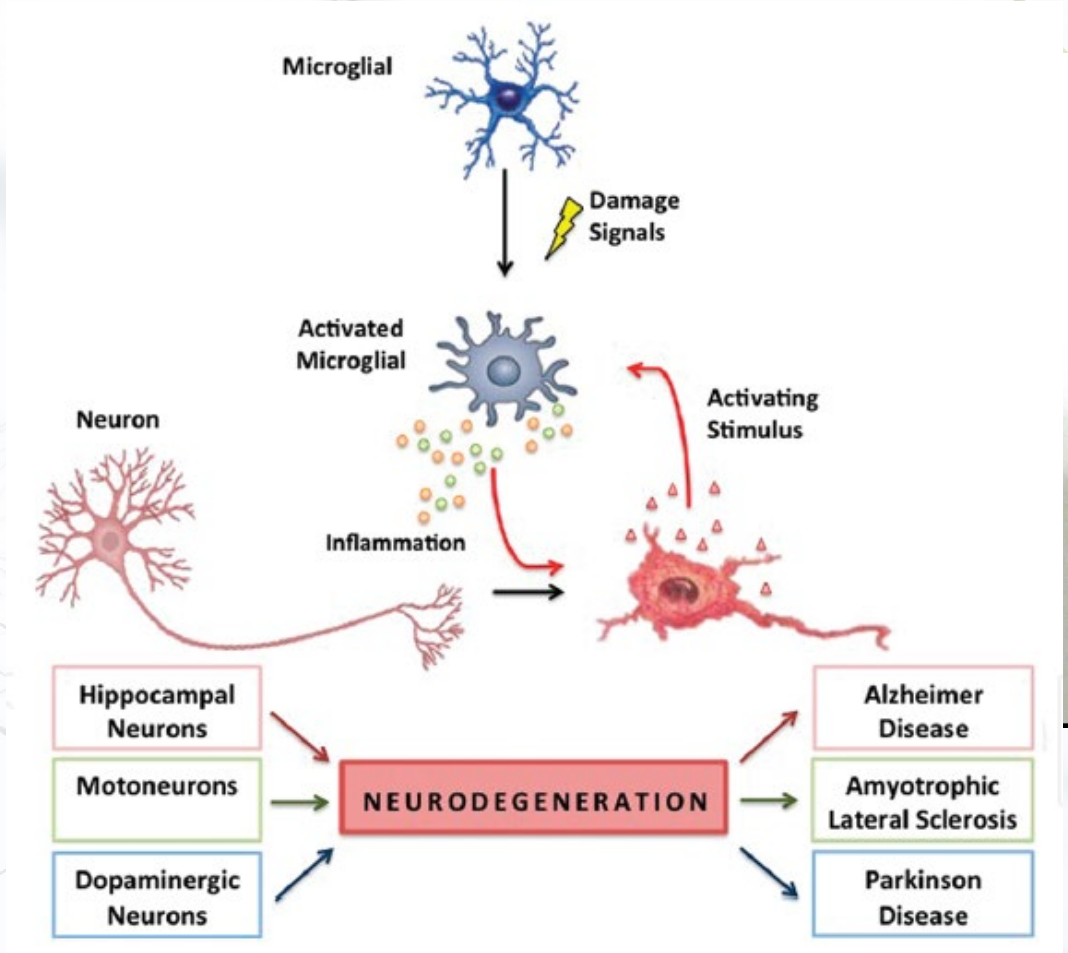
PMID: 34646826 PMCID: PMC8502923 DOI: 10.3389/fcell.2021.732820

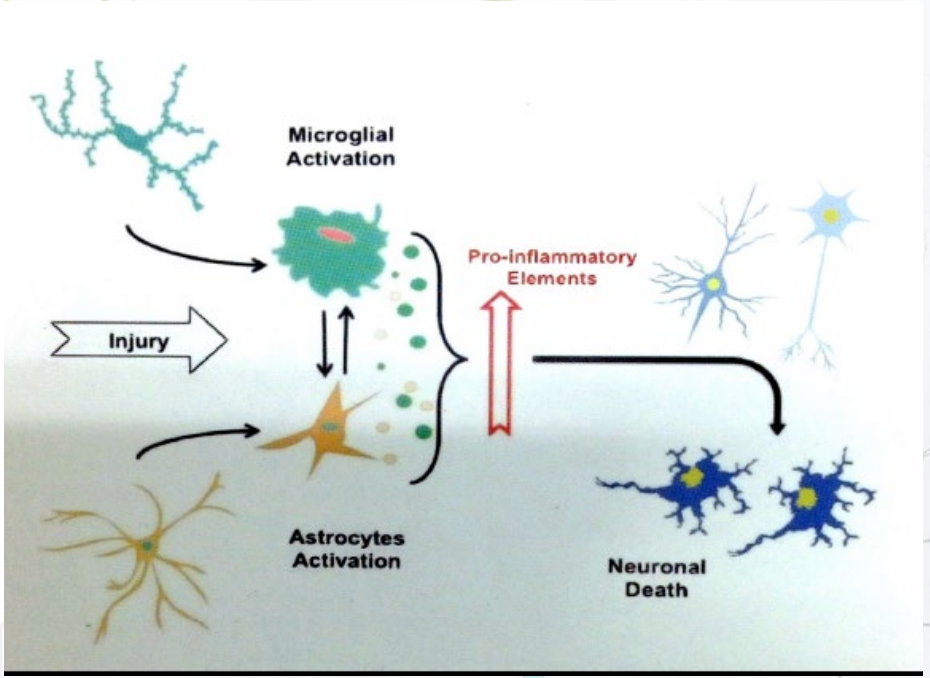
The neurovascular unit (NVU) is a complex multi-cellular structure consisting of endothelial cells (ECs), neurons, glia, smooth muscle cells (SMCs), and pericytes. Each component is closely linked to each other, establishing a structural and functional unit, regulating central nervous system (CNS) blood flow and energy metabolism as well as forming the blood-brain barrier (BBB) and inner blood-retina barrier (BRB



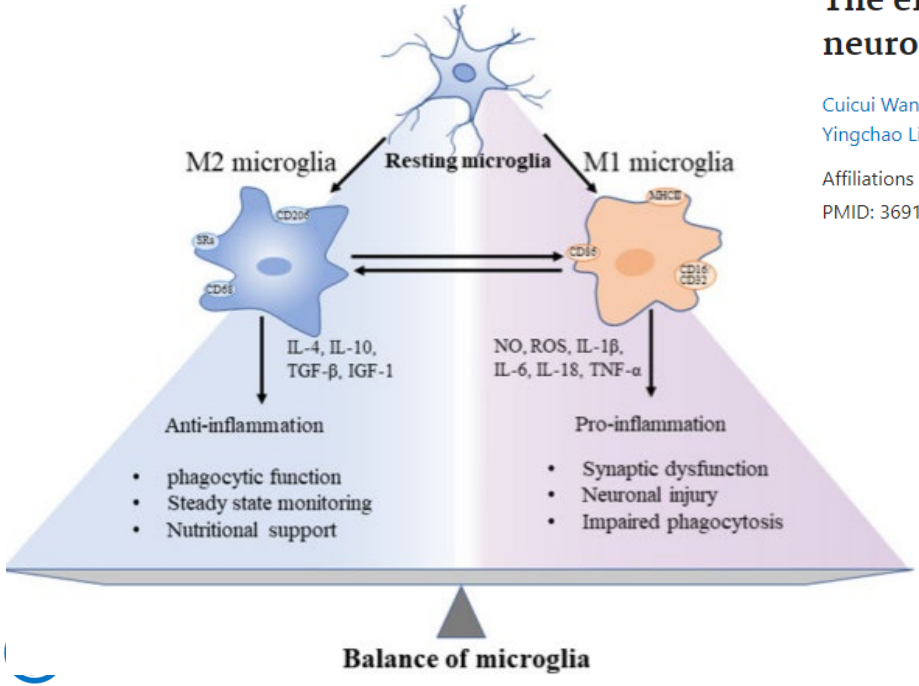

Alzheimer's disease
Neurotoxicity
Epicatechin
β amyloid plague
Cholinergic neuron
β amyloid
APP
ROS
NO
PGE2
TNFα
IL-1β
IL-6
β amyloid aggregates
Neuroinflammation
Activation
Catechin, Genistein, Luteolin
iNOS
COX-2
NAPDH oxidase
NF-κB
AP-1
Microglia
TNFα, IL-1β
β amyloid plague
Activated astrocyte

Microglia the working class cell of the brain





Il processo di attivazione microgliale è un fenomeno complesso, caratterizzato dall'acquisizione di diversi fenotipi funzionali, schematicamente rappresentati dai fenotipi M1 e M2, associati rispettivamente a funzioni neuro-tossiche e neuro-protettive.



The effects of microglia-associated neuroinflammation on Alzheimer's disease

Cuicui Wang [1], Shuai Zong [1], Xiaolin Cui [2], Xueying Wang [1], Shuang Wu [2], Le Wang [1], Yingchao Liu [1], Zhiming Lu [1]

Affiliations + expand

PMID: 36911732 PMCID: PMC9992739 DOI: 10.3389/fimmu.2023.1117172

Hindawi
Journal of Immunology Research
Volume 2018, Article ID 4784268, 12 pages
https://doi.org/10.1155/2018/4784268

Microglia in the CNS is heterogeneous with different functional phenotypes. Resting microglia are converted to active state of M1 or M2 phenotypes**. M1 phenotype is proinflammatory and M2 phenotype is neuroprotective, immunosuppressive and anti-inflammatory** and helps in tissue healing process.
M1 microglia predominates
at the site of injury than M2 microglia. Recently, M1/M2 paradigm of microglial activation has been extensively studied in neurodegenerative diseases to understand the role of microglia in neuroprotection and neurodegeneration . Microglial activation can be classified into classical activation and alternative activation based upon the nature of activation. Classical activation of microglia leads to the release of proinflammatory mediators such as IL-1β, IL-6, TNF-α, nitric oxide (NO), ROS and proteases. Microglia in this polarization state is called M1 phenotype. Microglia in the state of alternative activation is called M2 phenotype and is associated with neuroprotection and is anti-inflammatory.
Anti-inflammatory cytokines IL-4, IL-13, IL-10 and TGF-β from M2 microglia antagonize the activities of proinflammatory cytokines to re-establish normal condition.
The ratio of M1 and M2 microglial activation is altered in neurodegenerative diseases and therefore M1/M2 switching may help therapeutic effectiveness in neurodegenerative diseases

Microglial cells can have a neuroprotective role:
- IL-4, IL-10;
- express the cannabinoid receptors CB1 and CB2

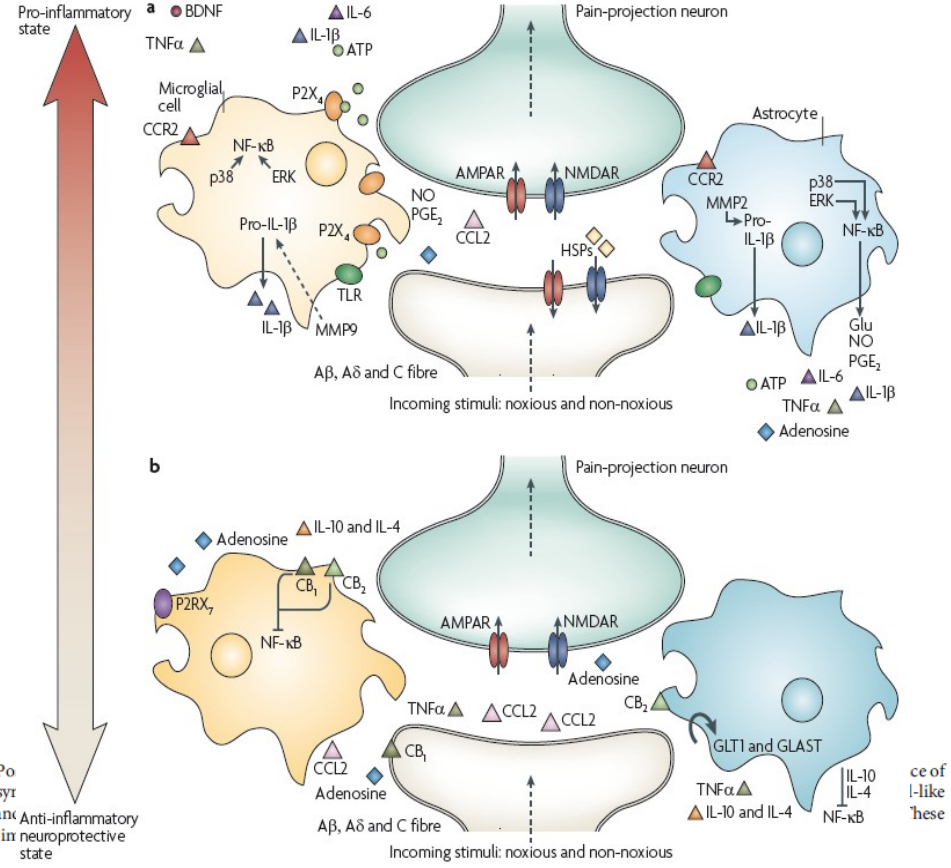


FIGURE 2: Po
specific α-syr
receptors an
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International Journal of *Molecular Sciences*

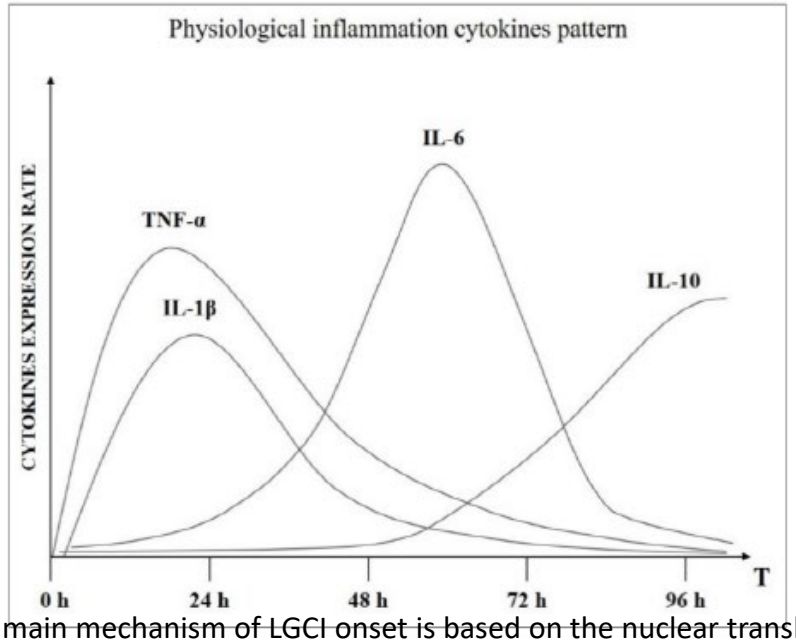
Int. J. Mol. Sci. **2021**, *22*, 5277. https://doi.org/10.3390/ijms22105277

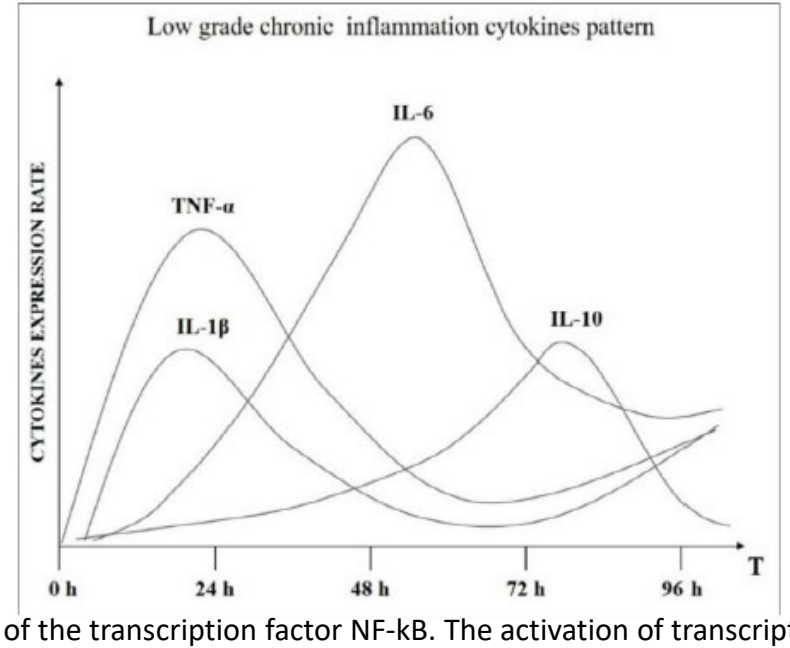
MDPI

Review

Regulation of Inflammatory Reaction in Health and Disease

Massimo Fioranelli [1,*], Maria Grazia Roccia [1], Dana Flavin [2] and Linda Cota [2]





The main mechanism of LGCI onset is based on the nuclear translocation of the transcription factor NF-kB. The activation of transcription and translation of specific pro-inflammatory genes is manifested by the release IL-1, TNF-α, and IL-6. At the same time, the oxidative damage produced by the inflammatory trigger reduces the production of AMPK, a fundamental inhibitory control factor of NF-kB translocation. The negative control function on the inflammatory cascade is thus lost.

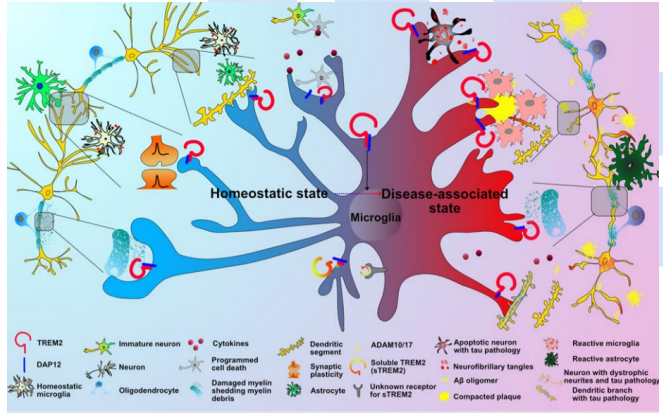
Neuroscientist. 2023 June ; 29(3): 302–316. doi:10.1177/10738584211040786.

Microglial TREM2 at the intersection of brain aging and Alzheimer's disease

Wenhui Qu[1], **Ling Li**[1,2,*]

[1]Graduate Program in Neuroscience, University of Minnesota, Minneapolis, MN 55455

[2]Department of Experimental and Clinical Pharmacology, University of Minnesota, Minneapolis, MN 55455



Biomedicine & Pharmacotherapy 165 (2023) 115218

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

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

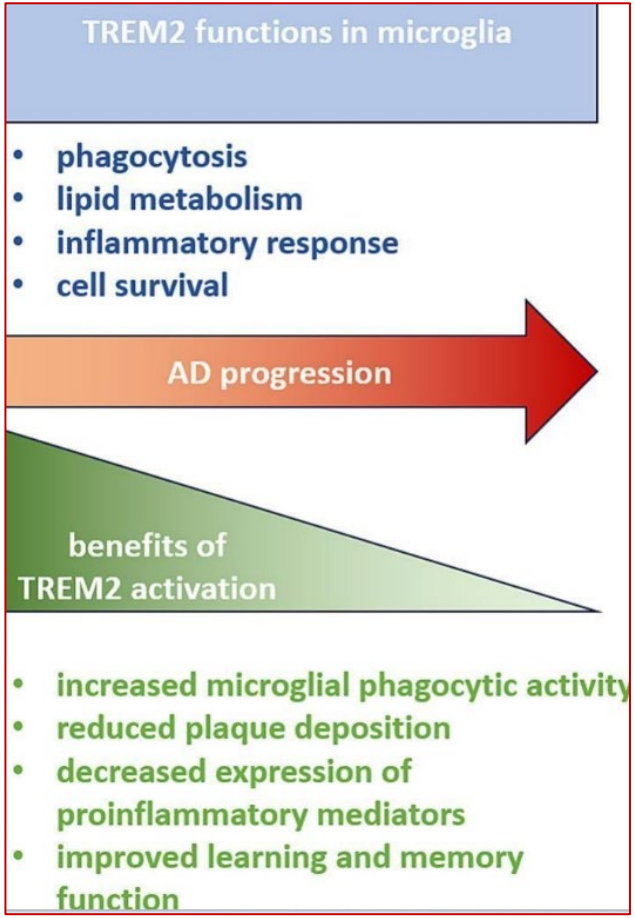
Review

TREM2: Potential therapeutic targeting of microglia for Alzheimer's disease

Yueran Li, Huifang Xu, Huifang Wang, Kui Yang, Jiajie Luan, Sheng Wang *

Department of Pharmacy, The First Affiliated Hospital of Wannan Medical College (Yijishan Hospital of Wannan Medical College), Wuhu, Anhui Province, China

Contoso



ELSEVIER

Molecular and Cellular Neuroscience
Volume 128, March 2024, 103917

TREM2 in Alzheimer's disease: Structure, function, therapeutic prospects, and activation challenges

Emilia Zgorzynska ✉

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https://doi.org/10.1016/j.mcn.2024.103917 ↗ Get rights and content ↗

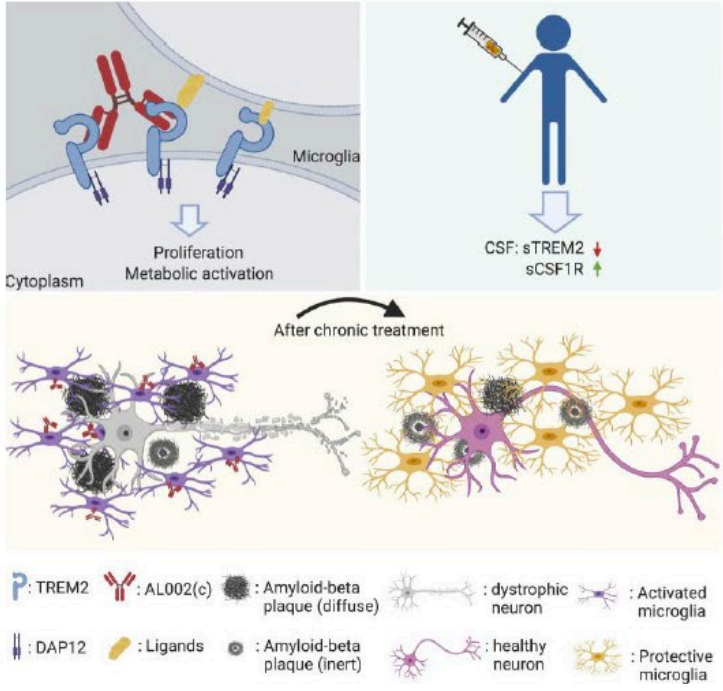
Highlights

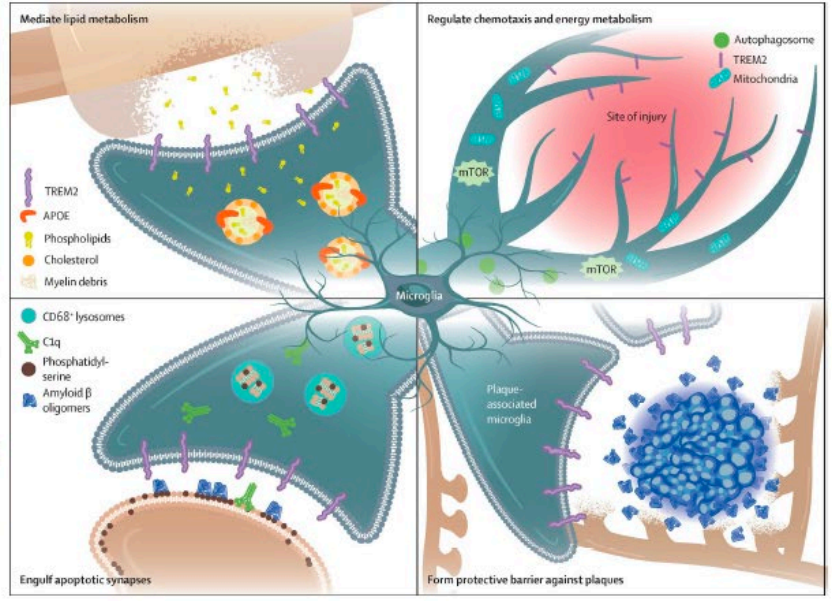
- Therapeutic targeting of TREM2 is context- and time-dependent.
- TREM2 activation may be beneficial in the early stages of AD but detrimental in the later stages.
- Development of TREM2-targeted treatments for AD requires consideration of its effects and potential risks.

Contoso

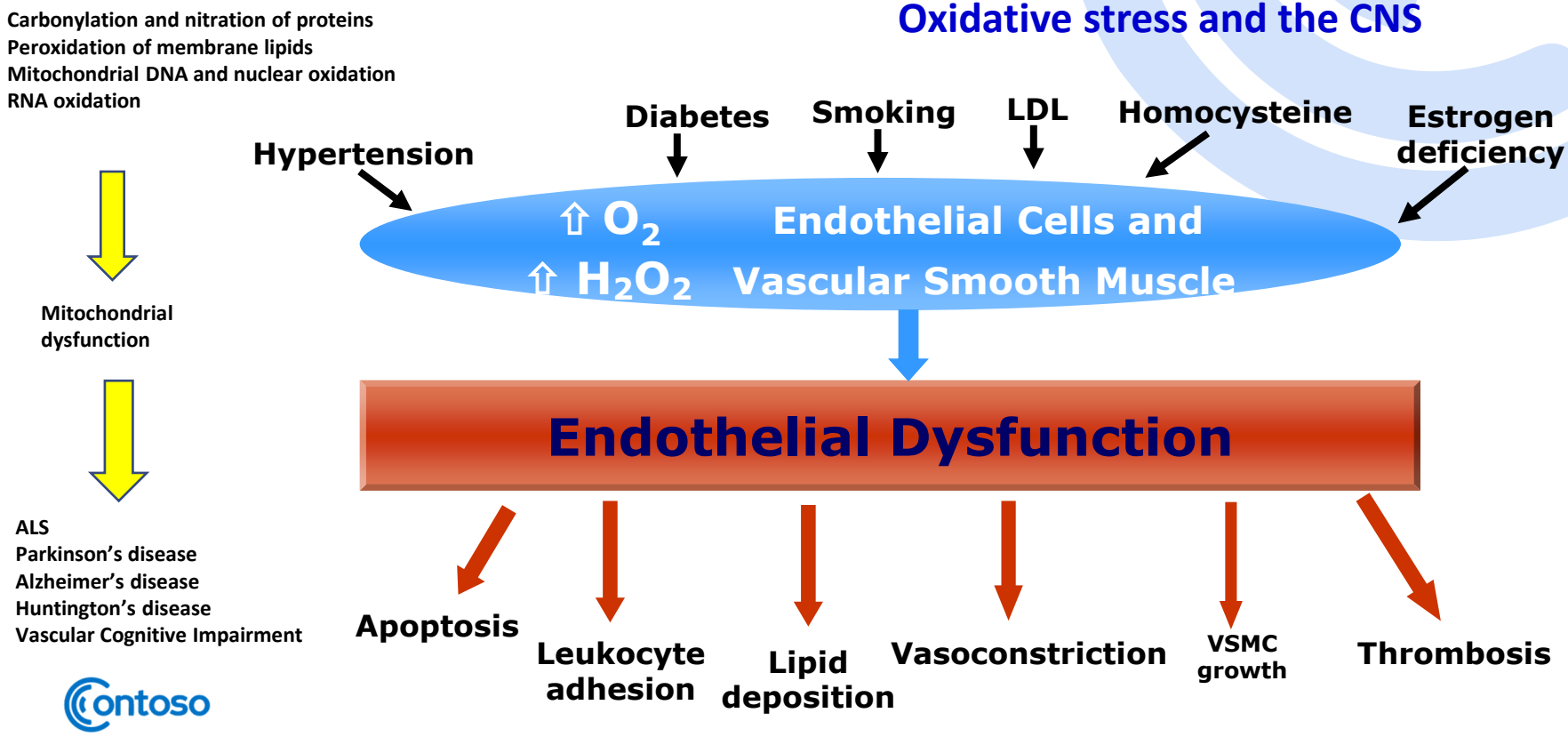
▸ J Exp Med. 2020 Jun 24;217(9):e20200785. doi: 10.1084/jem.20200785

Anti-human TREM2 induces microglia proliferation and reduces pathology in an Alzheimer's disease model





Oxidative Stress: Endothelial Dysfunction and CAD/Renal Risk Factors



Contoso

Contents lists available at ScienceDirect

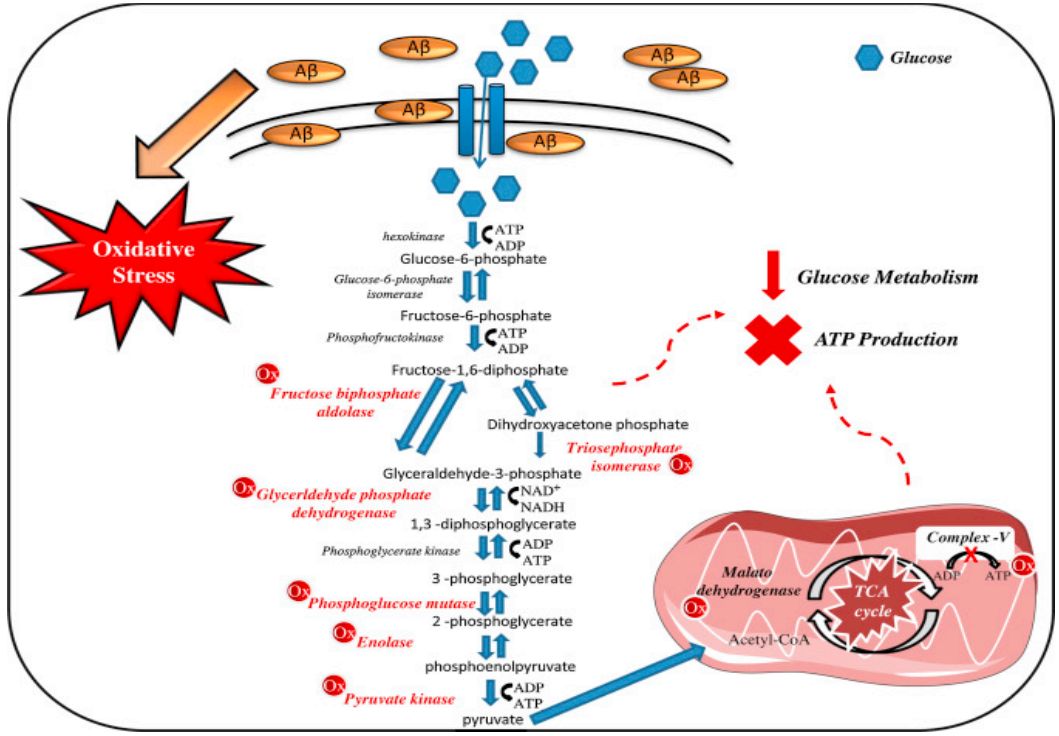
Brain Research Bulletin

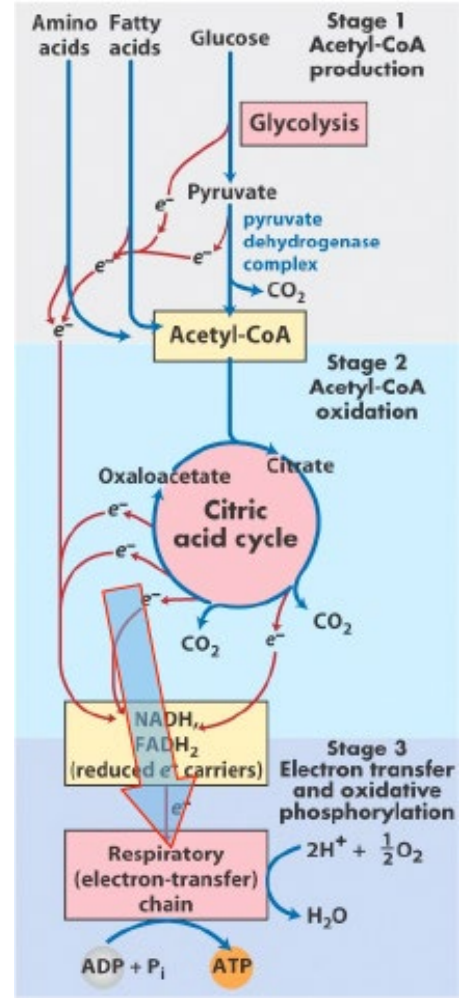
journal homepage: www.elsevier.com/locate/brainresbull

Research report

Oxidative stress, protein modification and Alzheimer disease

A. Tramutola [a], C. Lanzillotta [a], M. Perluigi [a], D. Allan Butterfield [b,*]





Brain Research Bulletin, 2016, Available online 15 June 2016

lo stress ossidativo è il prodotto di uno sbilanciamento

Per ragioni ancora poco note in alcune persone questi processi avvengono più precocemente e più rapidamente

- ✓ 1- sorgenti di specie ossidanti
- ✓ 2- meccanismi di difesa antiossidante
- ✓ 3- meccanismi di riparazione del danno

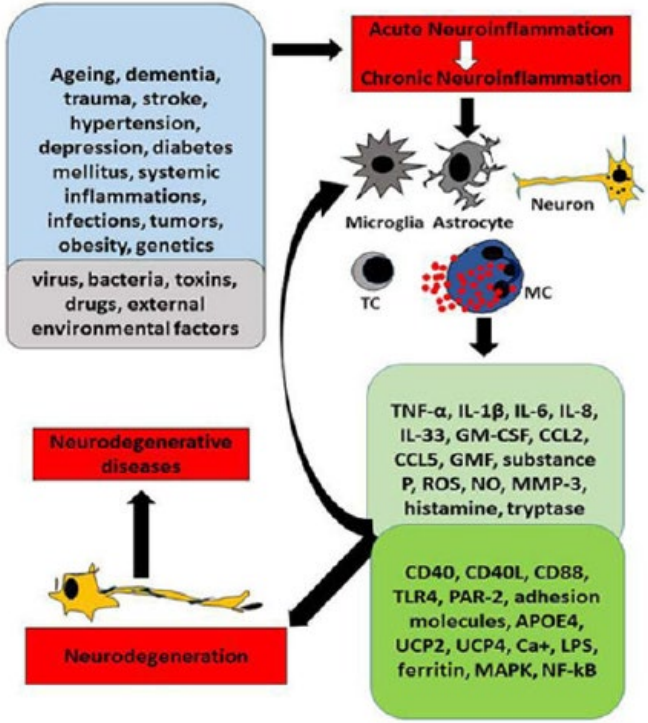
invecchiamento → stress ossidativo → mutazioni mtDNA

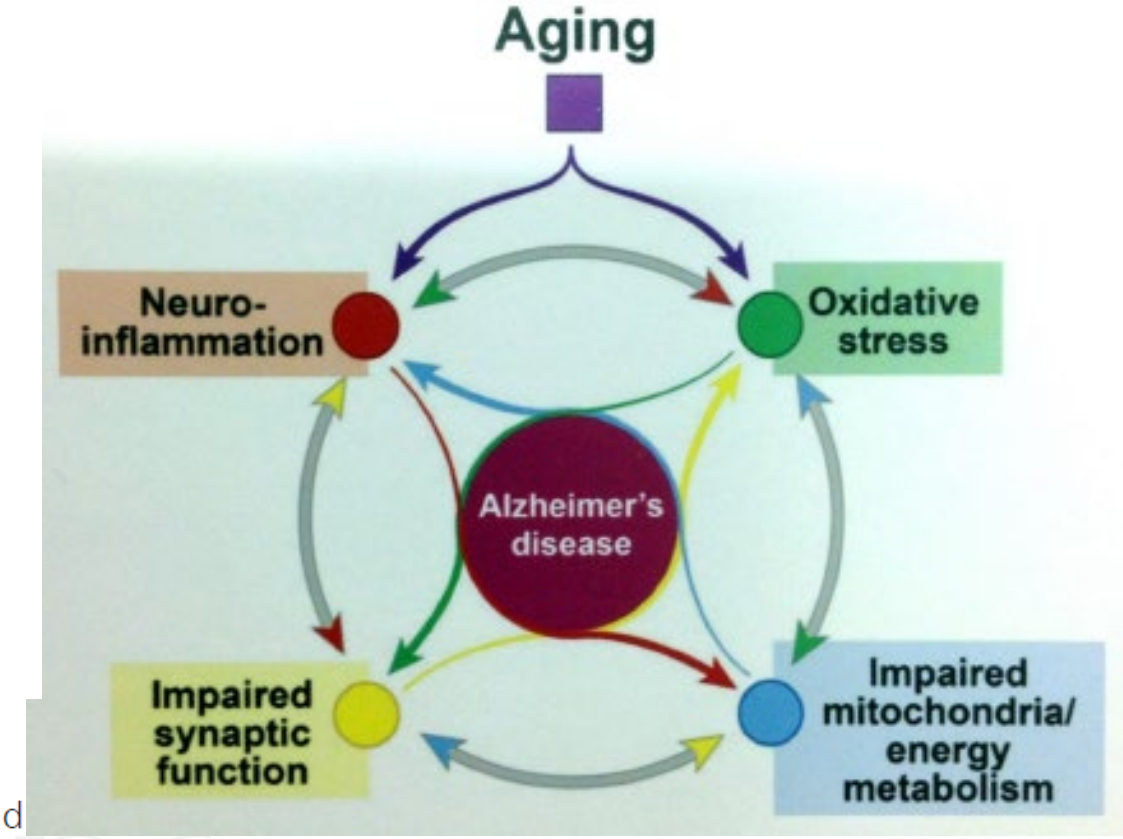
modelli animali che sovraesprimono enzimi antiossidanti (catalasi, MnSOD) vivono a lungo

conseguenze dello stress ossidativo

- ✓ Carbonilazione delle proteine
- ✓ Perossidazione dei lipidi di membrana
- ✓ Nitrazione delle proteine

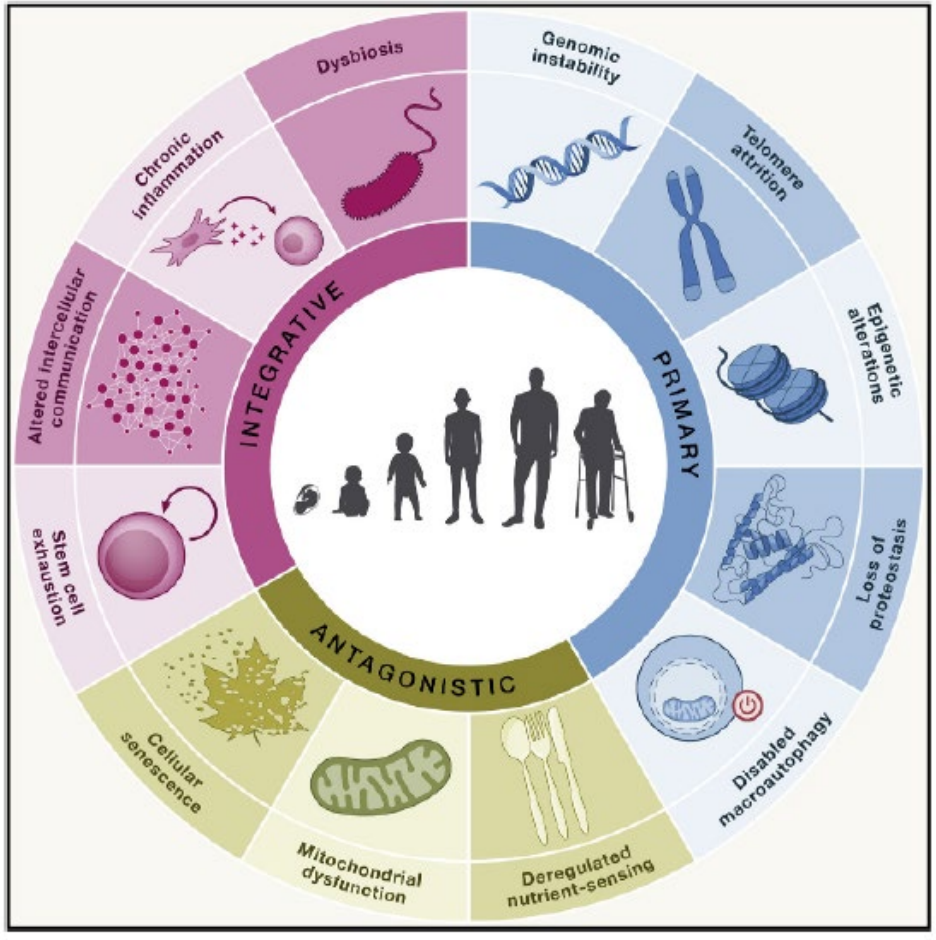
- ✓ Ossidazione del mtDNA
- ✓ Ossidazione del DNA nucleare
- ✓ Ossidazione dell'RNA

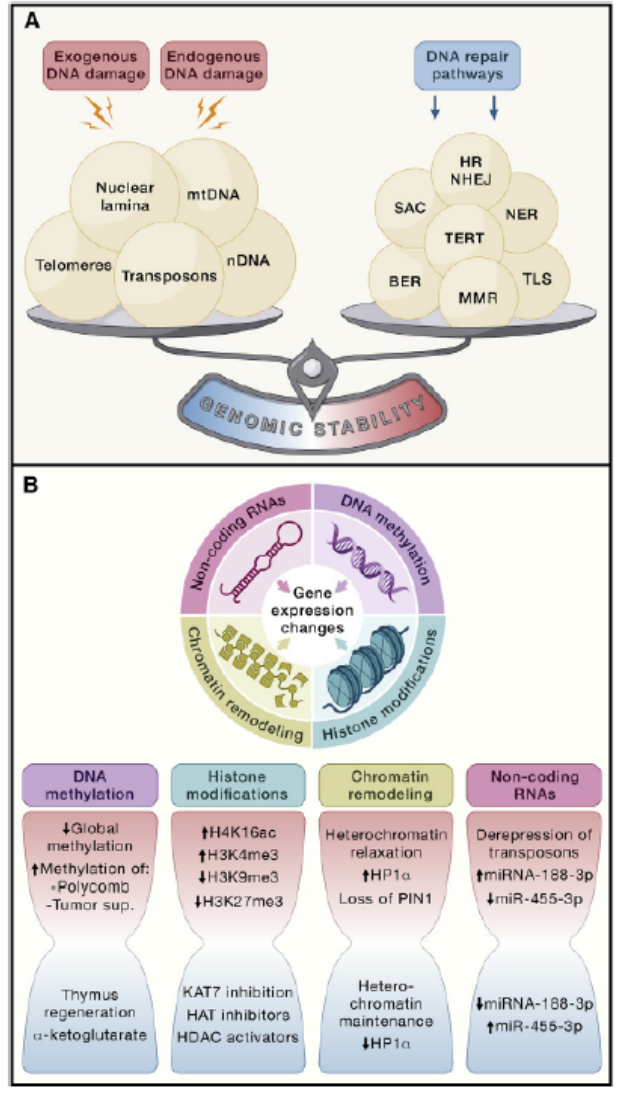


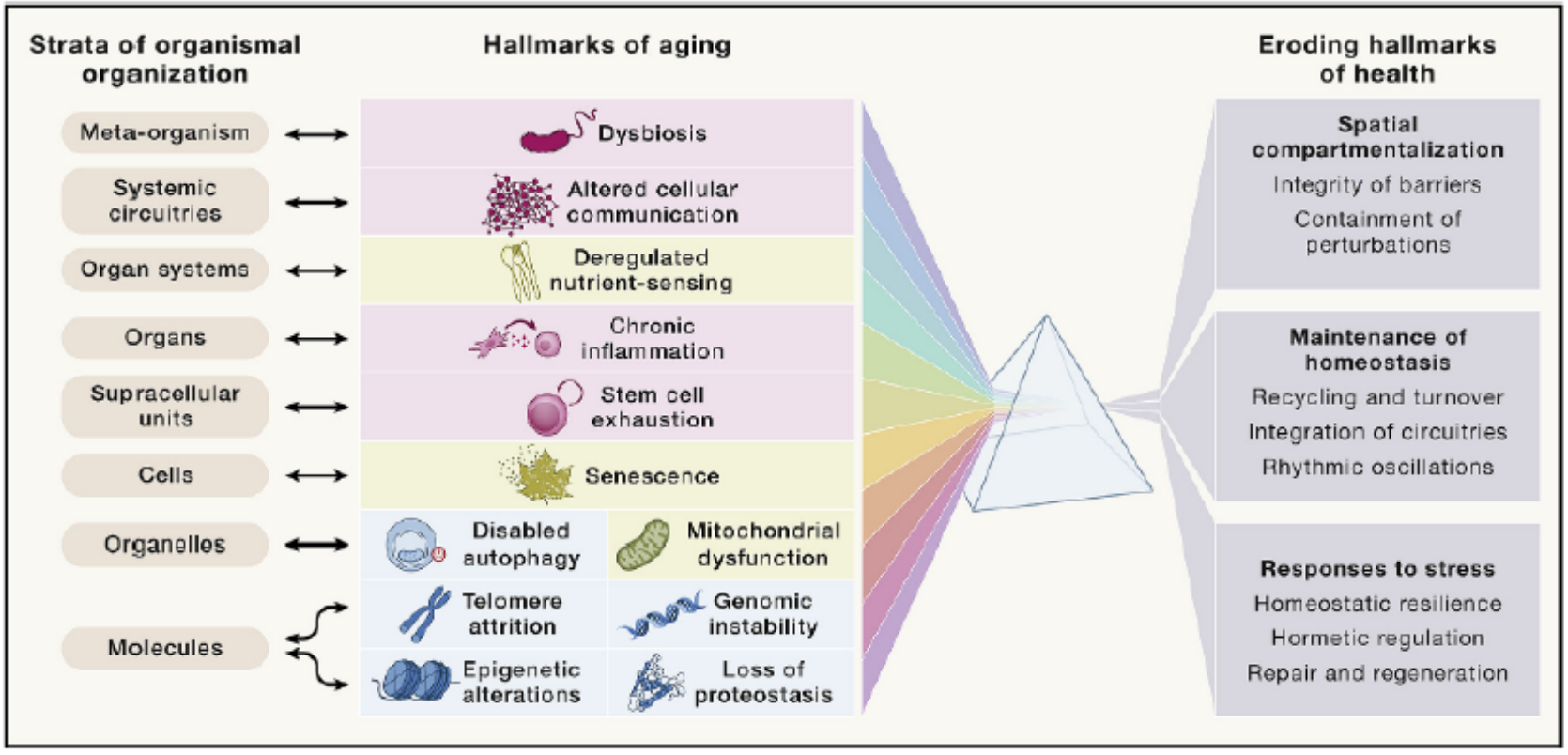


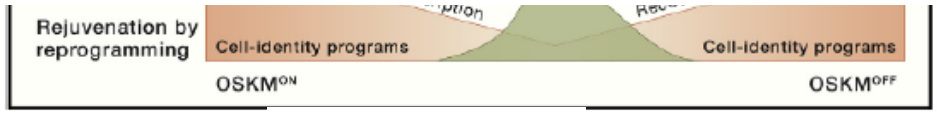
Inelia Morales, Gonzalo A. Farías, Nicole Cortes and Ricardo B. Maccioni

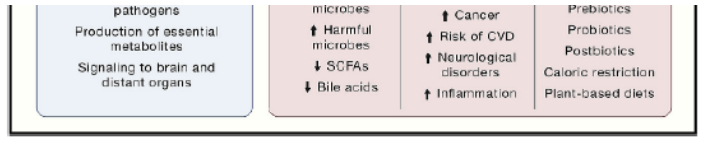
Cell *186*, January 19, 2023 © 2022 Elsevier Inc.











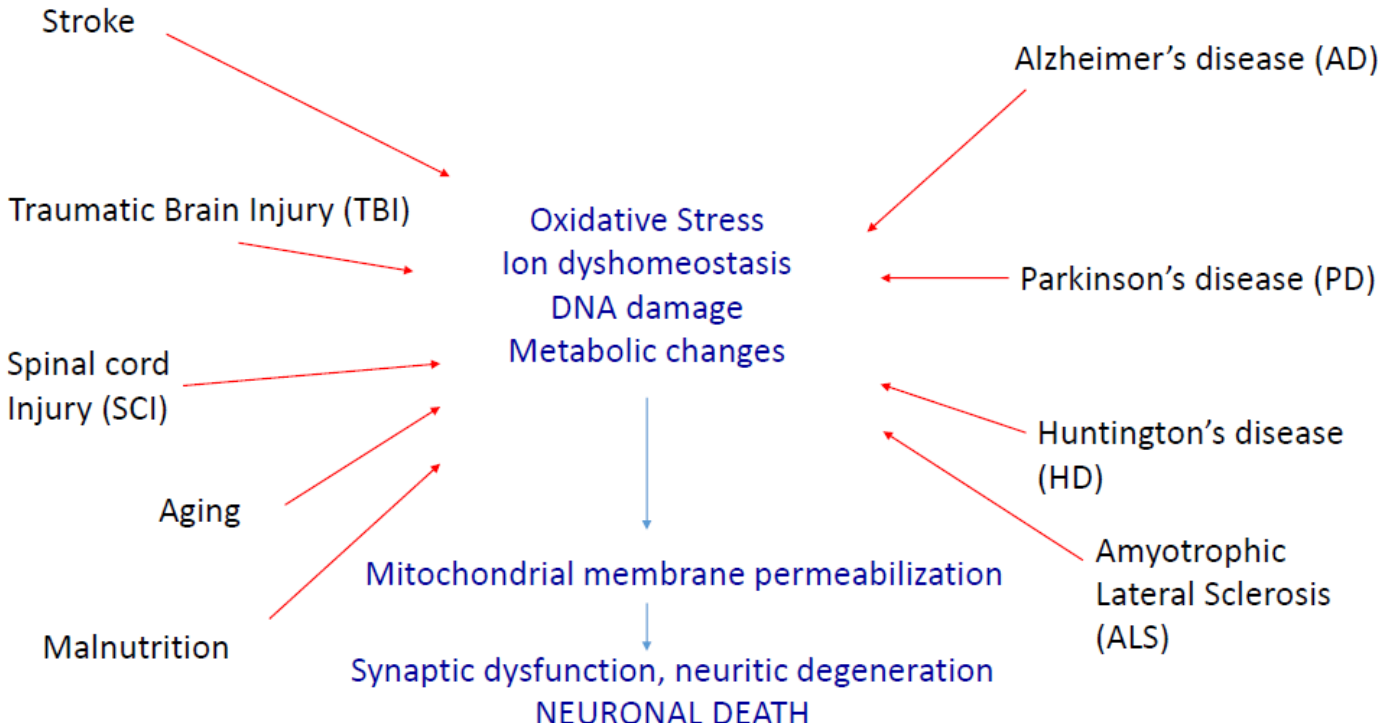
Cell *186*, January 19, 2023

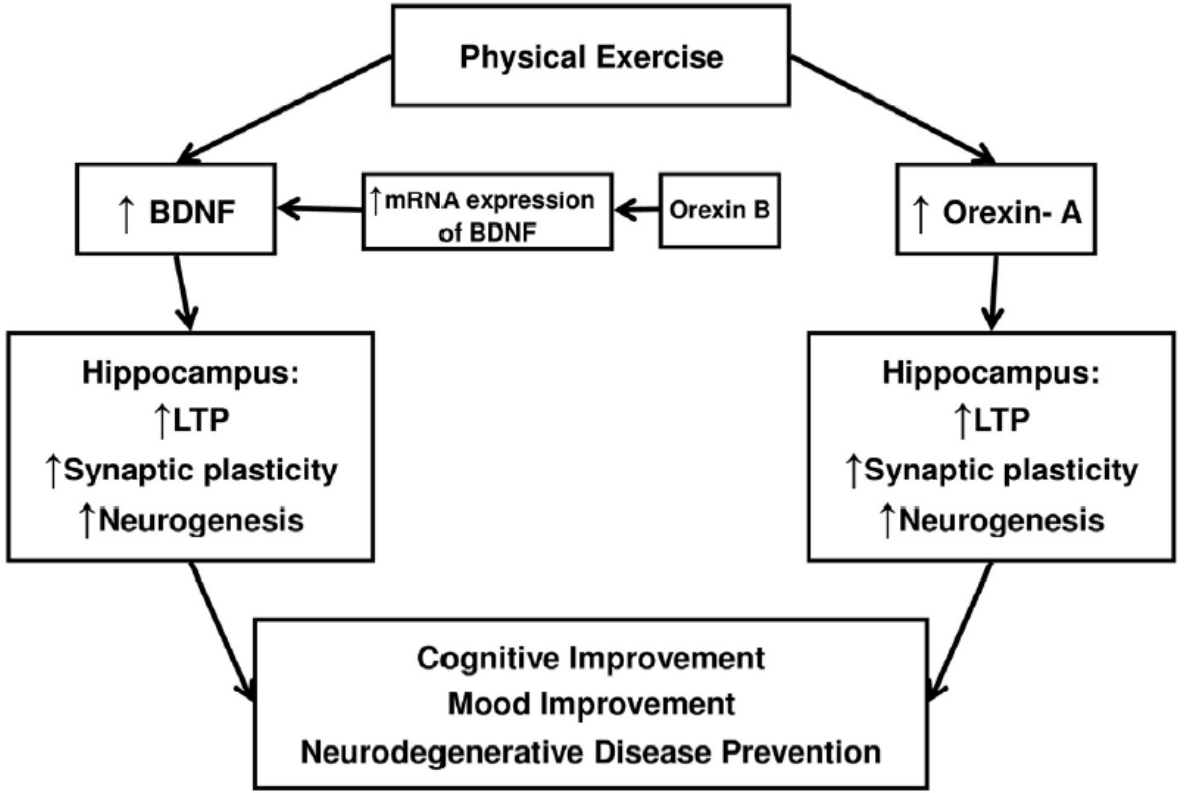
Review Article

NEUROLOGY AND NEUROBIOLOGY | ISSN 2613-7828

From Neuroinflammation to Neuroprotection: Focus on Potential New Therapeutic Targets in Cognitive Impairment

Pietro Gareri[1], Antonino Maria Cotroneo[2] and Valeria Graziella Laura Manfredi[3]*





STRATEGY FOR PUTATIVE NEUROPROTECTION

- Anti-oxidants
- Reduction of ROS production (low calorie diet)
- Anti-apoptotic compounds
- Anti-inflammatory agents
- Vaccination
- Promotion of trophic factors action
- Gene therapy enhancing expression of protective factors
- Stimulation of energy metabolism
- Physical (/cognitive?) exercise
- Nicotine ? (PD)
- Reducing excitotoxicity

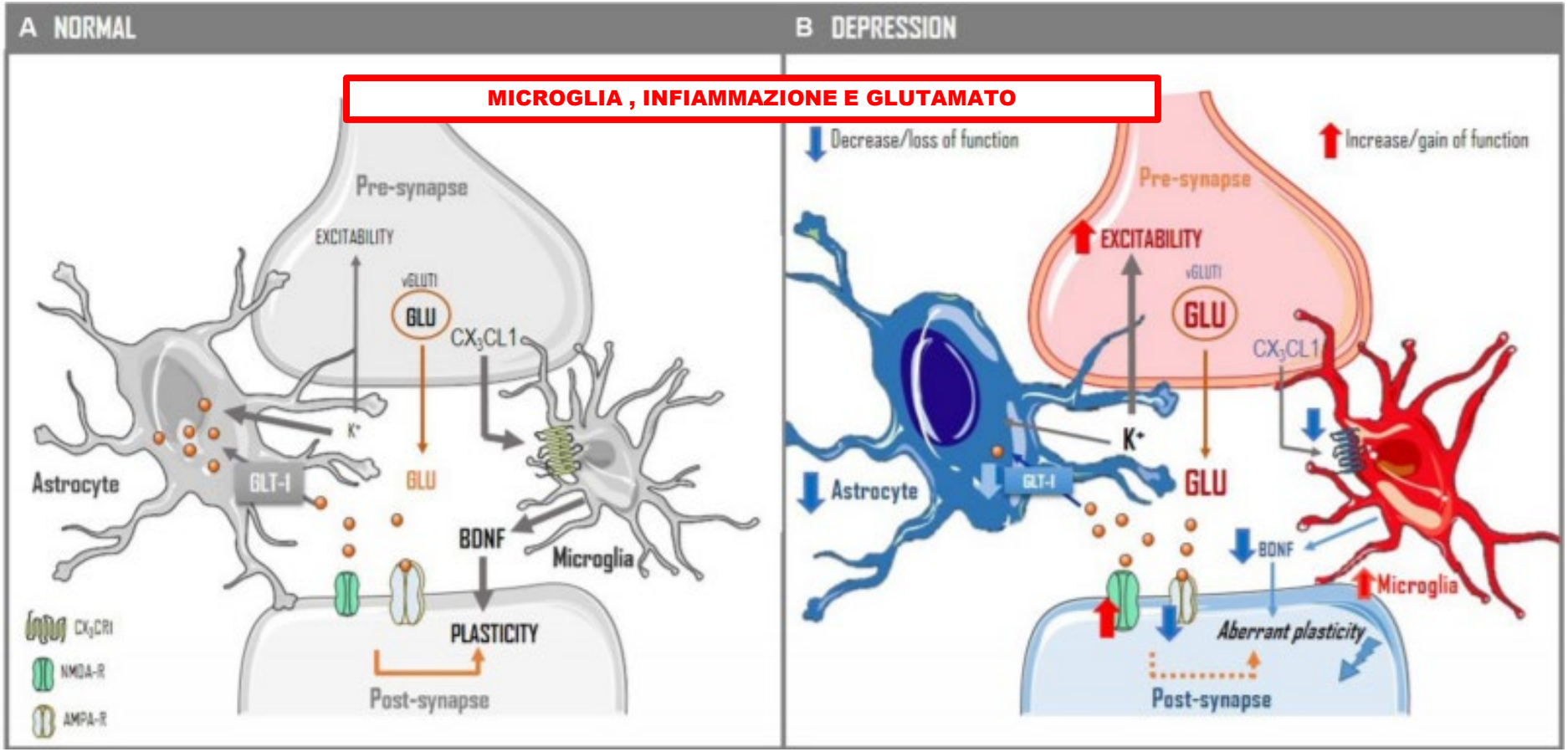
• Neuroplasticity

Neurorescue drugs, i.

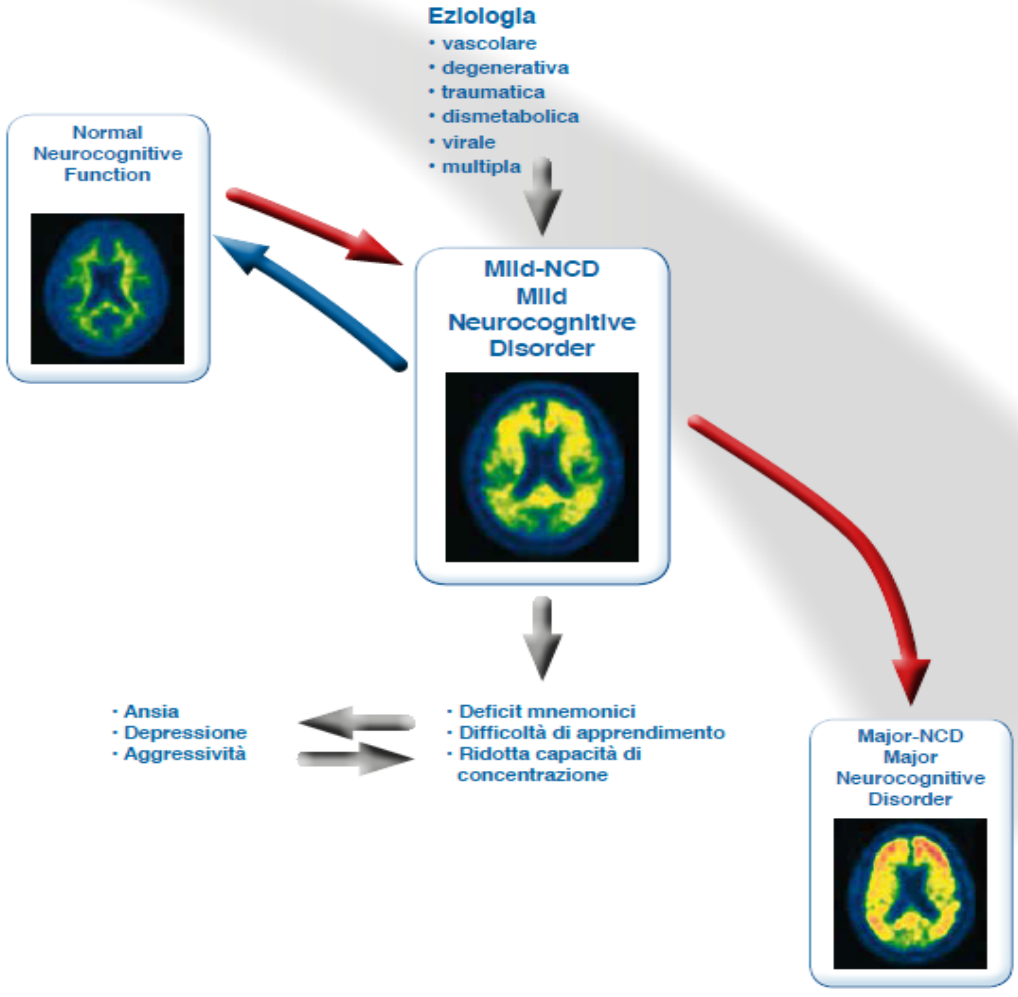
Depression as a Glial-Based Synaptic Dysfunction

Daniel Rial[1,2], Cristina Lemos[1], Helena Pinheiro[1], Joana M. Duarte[1],

Frontiers in Cellular Neuroscience January 2016



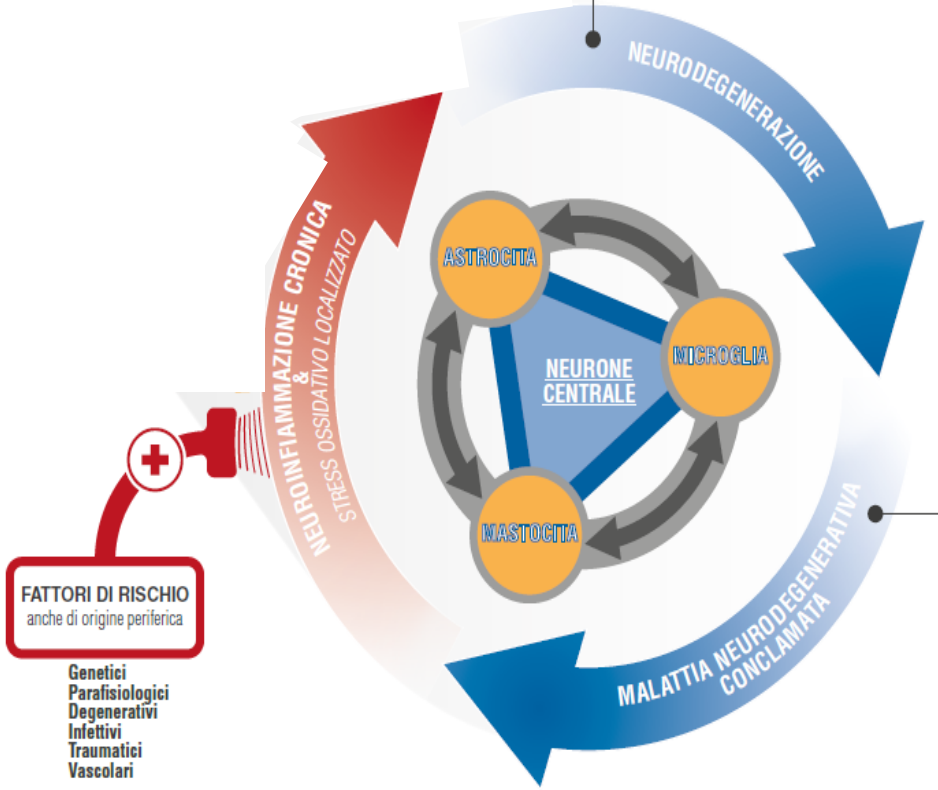
Grandi attenzioni da parte delle Neuroscienze sono oggi incentrate sull'associazione tra neuroinfiammazione centrale e declino cognitivo (Mild Neurocognitive Disorder – Mild-NCD).



Zone SNC
Ippocampo
Corteccia Entorinale e associativa
Lobo Temporale

Funzione Neuronale
Acetilcolina
Glutammato

SEGNI E SINTOMI CENTRALI	SEGNI E SINTOMI MOTORI E NEURO-SENSITIVI
• Disturbo della memoria e della concentrazione. • Disturbi affettivi (depressione, ansia, anedonia). • Alterazioni del comportamento (irritabilità, agitazione ecc.). • Diminuzione delle riserve cognitive. • Insonnia. • Delirium (post-operatorio, post-infettivo, post-emozionale).	• Negligenza Spaziale Unilaterale (NSU). • Alterazioni del movimento. • Disfagia neurogena. • Dolore centrale. • Disestesie e parestesie tattili e termo-dolorifiche.



European Journal of Nuclear Medicine and Molecular Imaging (2018) 45:1432–1441
https://doi.org/10.1007/s00259-018-3984-5

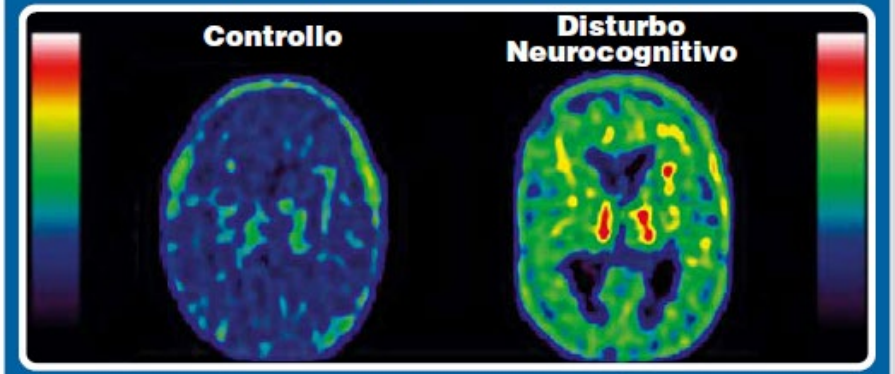
ORIGINAL ARTICLE

Parametric mapping using spectral analysis for ^{11}C-PBR28 PET reveals neuroinflammation in mild cognitive impairment subjects

Zhen Fan[1] · Melanie Dani[1] · Grazia D. Femminella[1] · Melanie Wood[1] · Valeria Calsolaro[1] · Mattia Veronese[2] · Federico Turkheimer[2] · Steve Gentleman[1] · David J. Brooks[1,3] · Rainer Hinz[4] · Paul Edison[1]

Neuroimaging della Neuroinfiammazione in pazienti con Disturbo Neurocognitivo Lieve*

**Mild Cognitive Impairment (MCI) secondo la precedente classificazione*



Distribuzione spaziale della neuroinfiammazione in soggetto sano (sinistra) e affetto da Disturbo Neurocognitivo Lieve (destra), valutata mediante PET con un radioligando marcatore dell'iperattività microgliale (11C–PBR28).
La aree giallo-rosse dell'**immagine PET** (visibili solo a destra) rilevano la presenza di **neuroinfiammazione** a livello di **ippocampo**, **talamo** e **vari distretti della corteccia cerebrale**.[1; 2]

Contoso

Disturbi
Neurocognitivo-comportamentali della sfera:

Sfera della comunicazione verbale
- Difficoltà di linguaggio
- Difficoltà di comprensione del linguaggio
- Difficoltà nell'associare agli oggetti il loro nome
- Inappropriato uso dei vocaboli

Sfera Mnesica
- Deficit memoria breve e lungo term.
- Perdita della memoria associativa
- Perdita memoria topografica
- Ridotta capacità di concentrazione

Sfera Cognitiva
- Attenzione e velocità di elaborazione
- Scarso rendimento
- Stato confusionale
- Ridotta capacità di sintesi

Sfera dell'affettività
- Ansia
- Depressione
- Aggressività
- Sensazione di paura
- Angoscia

Sfera percettivo-motoria
-Aprassie
-Agnosie
-Percezione visiva

Sfera psico-sociale
- Scarsa socializzazione
- Anedonia
- Ipocondria
- Pessimismo
- Cambiamento della personalità

Contoso

Esiste una stretta **correlazione tra Disturbi Depressivi e Disturbi Cognitivi**, determinata dalla presenza di **Neuroinfiammazione in diversi distretti della Corteccia Cerebrale**.

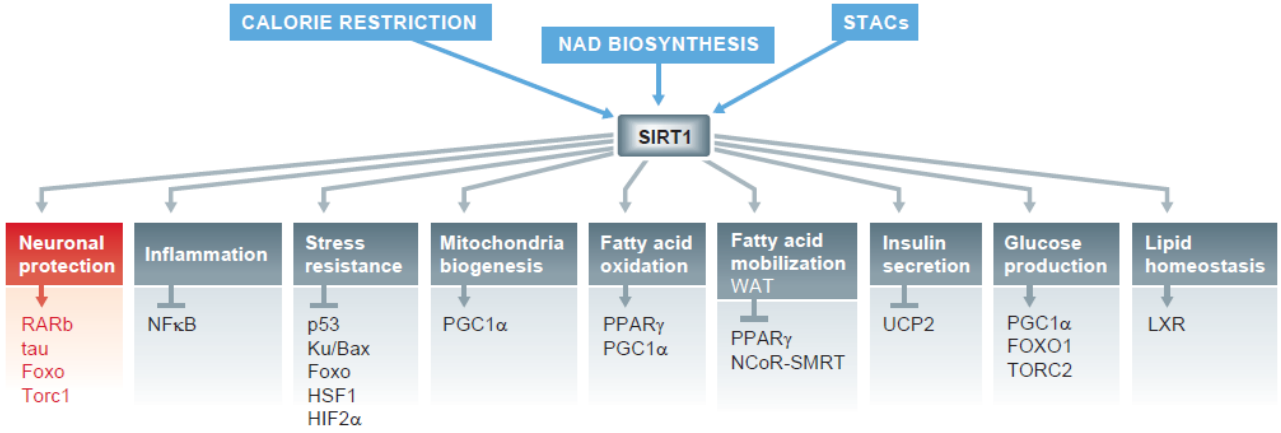
Short report

Neuroinflammatory and morphological changes in late-life depression: the NIMROD study

L. Su, Y. O. Faluyi, Y. T. Hong, T. D. Fryer, E. Mak, S. Gabel, L. Hayes, S. Soteriades, G. B. Williams, R. Arnold, L. Passamonti, P. Vázquez Rodríguez, A. Surendranathan, R. W. Bevan-Jones, J. Coles, F. Aigbirhio, J. B. Rowe* and J. T. O'Brien*

BJPsych The British Journal of Psychiatry (2016) 209, 525–526. doi: 10.1192/bjp.bp.116.190165

Contoso



EMBO Mol Med (2013) 5, 344–352

Figure 1. The targets and interacting partners of SIRT1. SIRT1 has many targets that play roles in different molecular pathways including neuronal protection, inflammation, stress resistance, mitochondrial biogenesis, fatty acid oxidation and mobilization, insulin secretion, glucose production and lipid homeostasis. SIRT1 is activated by CR, NAD biosynthesis and small molecule sirtuin activators (STACs).

- Sirtuins are NAD^+-dependent histone deacetylases
- SIRT1 is the best characterized sirtuin expressed in neurons
- SIRT1 is protective against acute and chronic neurological diseases
- Deacetylation on histone and non-histone targets contributes to the protective effects of SIRT1
- The activity of SIRT1 is adjustable, making it a neuroprotective target.

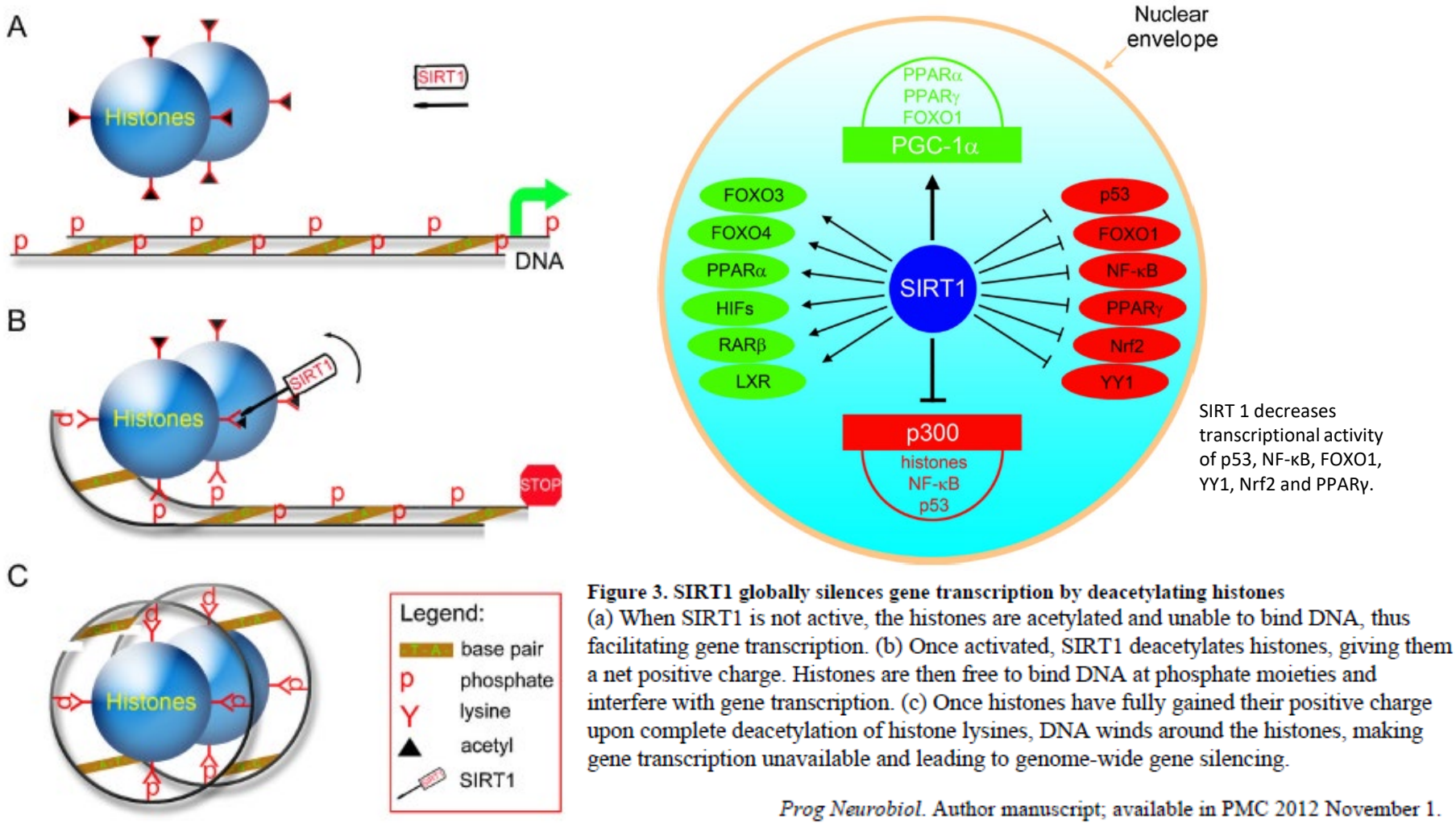
Protective effects and mechanisms of sirtuins in the nervous system

Feng Zhang[a,c,*], Suping Wang[a,c,*], Li Gan[b], Peter S. Vosler[c], Yanqin Gao[a,c], and Jun Chen[a,c,d]

Prog Neurobiol. 2011 November ; 95(3): 373–395.

Protective effects in:

AD
PD
Prion disease
ischemia
HD
MS
Cerebral



SIRT 1 decreases transcriptional activity of p53, NF-κB, FOXO1, YY1, Nrf2 and PPARγ.

Figure 3. SIRT1 globally silences gene transcription by deacetylating histones

(a) When SIRT1 is not active, the histones are acetylated and unable to bind DNA, thus facilitating gene transcription. (b) Once activated, SIRT1 deacetylates histones, giving them a net positive charge. Histones are then free to bind DNA at phosphate moieties and interfere with gene transcription. (c) Once histones have fully gained their positive charge upon complete deacetylation of histone lysines, DNA winds around the histones, making gene transcription unavailable and leading to genome-wide gene silencing.

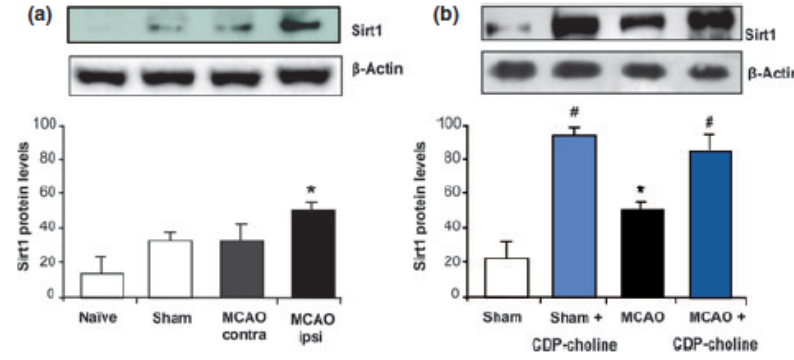
Prog Neurobiol. Author manuscript; available in PMC 2012 November 1.

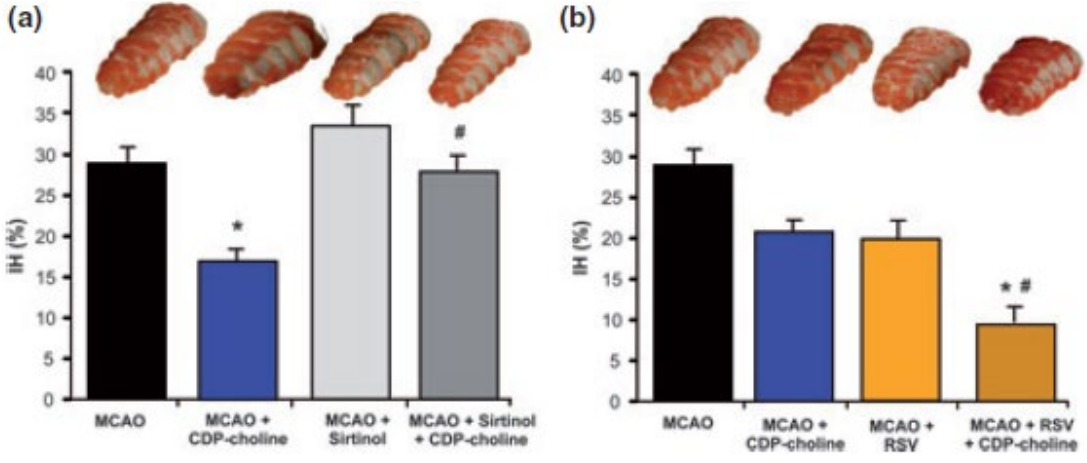
SIRTUIN 1 AND AD

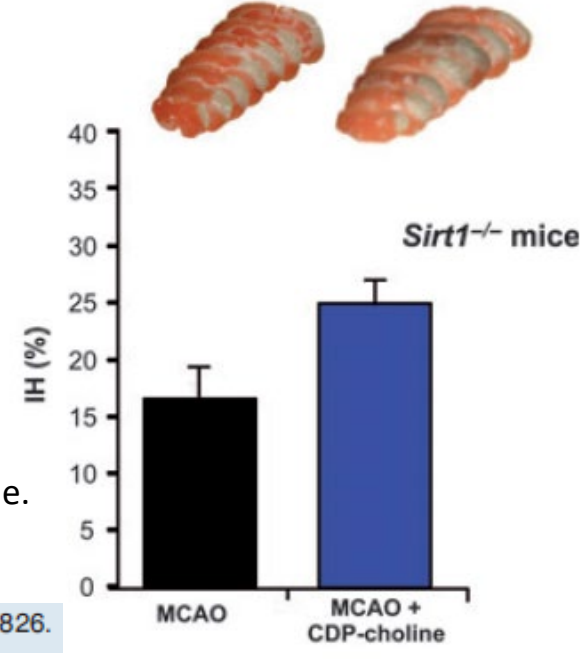
- Caloric restriction was shown to reduce amyloid plaques, one of the typical pathological hallmarks of the disease; the activation of SIRT1 may be a result of CR
- In an in vitro model, SIRT1 protects against microglia-dependent amyloid-beta (Aβ) toxicity through inhibiting NF-kB signaling
- SIRT1 is protective against Aβ plaque formation in animal models
- Overexpression of SIRT1 reduced Aβ production and Aβ plaques, whereas deleting SIRT1 increased Aβ levels.
- SIRT1 deacetylates RARβ and activates ADAM10 (α-secretase) transcription, leading to upregulated APP processing by α-secretase, resulting in reduced production of Aβ.

EMBO Mol Med (2013) 5, 344–352

Treatment with CDP-choline increased SIRT1 protein levels in brain concomitantly to neuroprotection.



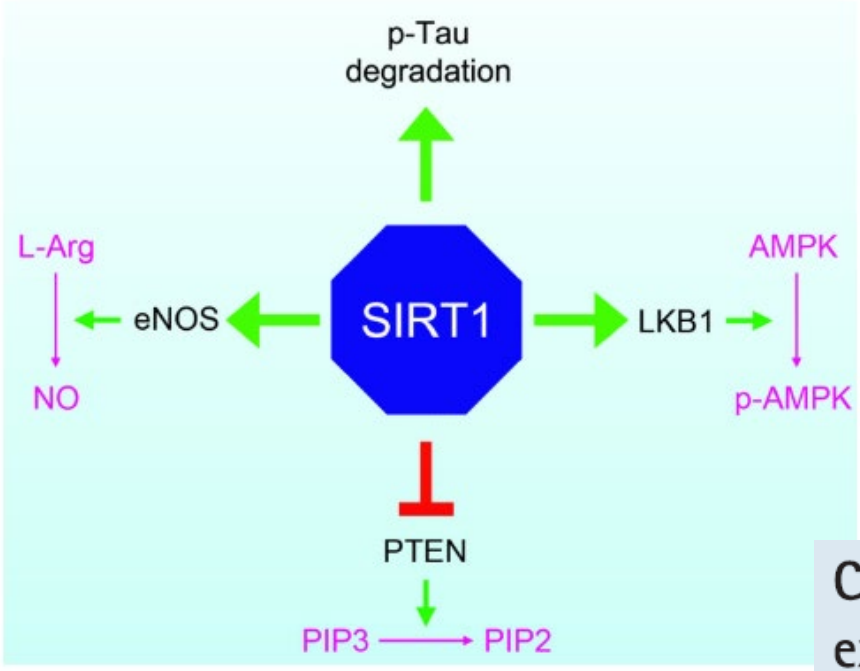




Treatment with sirtinol blocked the reduction in infarct volume caused by CDPcholine, whereas resveratrol elicited a strong synergistic neuroprotective effect with CDP-choline.

CDP-choline failed to reduce infarct volume in Sirt1-/- mice

J. Neurochem. (2013) **126**, 819–826.



Prog Neurobiol. Author manuscript; available in PMC 2012 November 1.

Figure 5. Cytosolic targets of SIRT1

In addition to its numerous actions in the nucleus, SIRT1 also has some newly discovered cytosolic targets. SIRT1 deacetylates and activates LKB1, leading to increased AMPK activity and attenuating ischemic brain injury. SIRT1 activity can also inhibit enzyme activity. Deacetylation of PTEN by SIRT1 inhibits the phosphatase's ability to bind and dephosphorylate PIP3, and results in unhindered activity of the neuroprotective PI3K/Akt signaling pathway. Deacetylation of eNOS stimulates the production of NO, a potent vasodilator. Putatively, this improves cerebral perfusion following ischemic stroke or subarachnoid hemorrhage. Finally, SIRT1 also deacetylates phosphorylated tau, facilitating its degradation and reducing neuronal death in models of Alzheimer's disease.

Journal of Neurochemistry JNC

JOURNAL OF NEUROCHEMISTRY | 2013 | 126 | 819–826 doi: 10.1111/jnc.12269

Citicoline (CDP-choline) increases Sirtuin1 expression concomitant to neuroprotection in experimental stroke

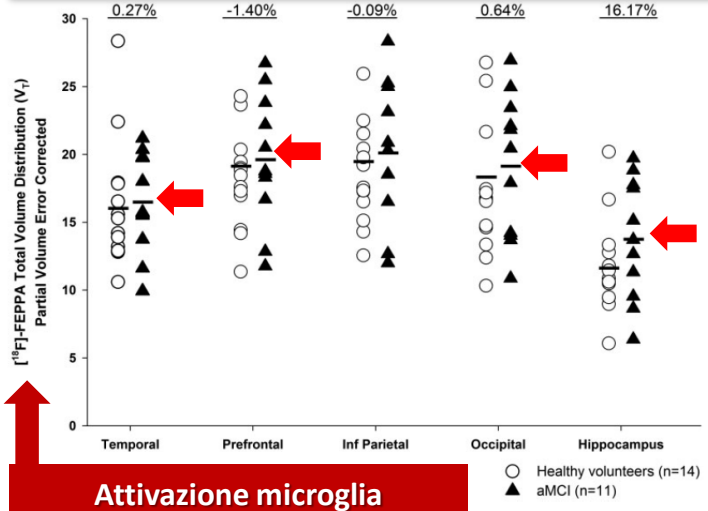
Olivia Hurtado,*,[1] Macarena Hernández-Jiménez,*,[1] Juan G. Zarruk,* María I. Cuartero,* Iván Ballesteros,* Guadalupe Camarero,* Ana Moraga,* Jesús M. Pradillo,† María A. Moro* and Ignacio Lizasoain*

Imaging microglial activation and amyloid burden in amnestic mild cognitive impairment

Dunja Knezevic[1,2], Nicolaas Paul LG Verhoeff[1,3], Sina Hafizi[1], Antonio P Strafella[1,2,4], Ariel Graff-Guerrero[1,2], Tarek Rajji[1,2], Bruce G Pollock[1,2], Sylvain Houle[1,2], Pablo M Rusjan[1,2] and Romina Mizrahi[1,2]

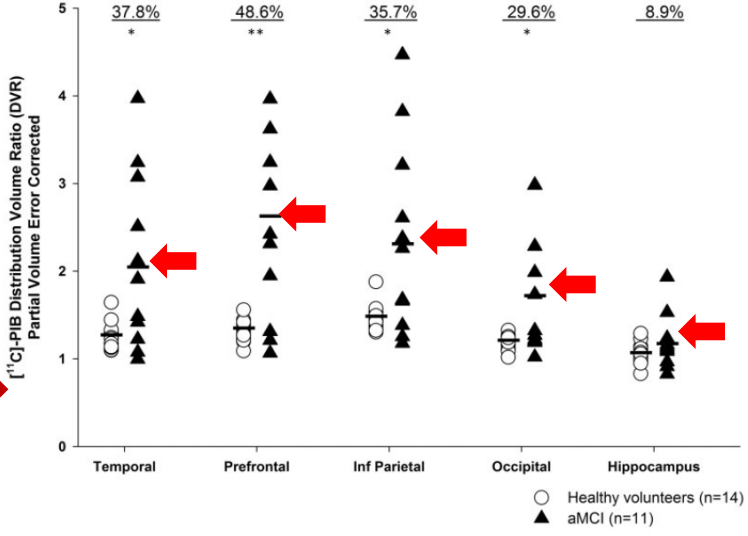
JCBFM

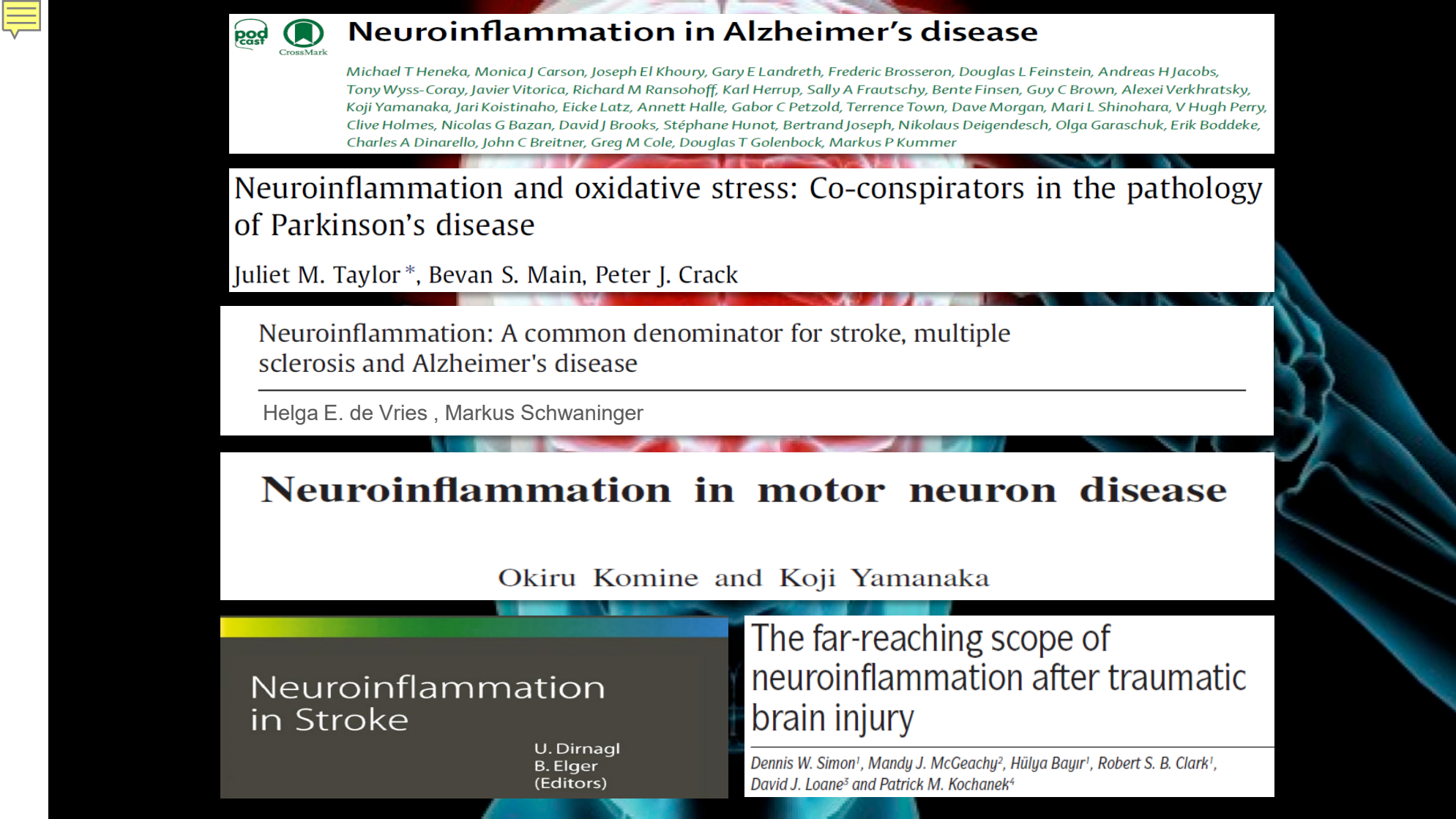
Knezevic et al., 2017



Attivazione microglia maggiore in soggetti con MCI

Accumulo beta amiloide maggiore in soggetti con MCI




Neuroinflammation in Alzheimer's disease
Michael T Heneka, Monica J Carson, Joseph El Khoury, Gary E Landreth, Frederic Brosseron, Douglas L Feinstein, Andreas H Jacobs, Tony Wyss-Coray, Javier Vitorica, Richard M Ransohoff, Karl Herrup, Sally A Frautschy, Bente Finsen, Guy C Brown, Alexei Verkhratsky, Koji Yamanaka, Jari Koistinaho, Eicke Latz, Annett Halle, Gabor C Petzold, Terrence Town, Dave Morgan, Mari L Shinohara, V Hugh Perry, Clive Holmes, Nicolas G Bazan, David J Brooks, Stéphane Hunot, Bertrand Joseph, Nikolaus Deigendesch, Olga Garaschuk, Erik Boddeke, Charles A Dinarello, John C Breitner, Greg M Cole, Douglas T Golenbock, Markus P Kummer
Neuroinflammation and oxidative stress: Co-conspirators in the pathology of Parkinson's disease
Juliet M. Taylor *, Bevan S. Main, Peter J. Crack
Neuroinflammation: A common denominator for stroke, multiple sclerosis and Alzheimer's disease
Helga E. de Vries , Markus Schwaninger
Neuroinflammation in motor neuron disease
Okiru Komine and Koji Yamanaka
Neuroinflammation in Stroke
U. Dirnagl
B. Elger
(Editors)
The far-reaching scope of neuroinflammation after traumatic brain injury
Dennis W. Simon[1], Mandy J. McGeachy[2], Hülya Bayır[1], Robert S. B. Clark[1], David J. Loane[3] and Patrick M. Kochanek[4]

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Medical Hypotheses (2003) **61**(1), 110–113

doi:10.1016/S0306-9877(03)00141-5

Brain-derived neurotrophi
a bridge between major
depression and Alzheimer

Shih-Jen Tsai

Veterans General Hospital, Taipei, Taiwan, ROC
National Yang-Ming University, Taiwan, ROC

NEUROTROFISMO E DEPRESSIONE

Summary Cognitive impairment is common in major depres
increased risk for development of Alzheimer's disease (AD). F
AD patients. This apparent convergence suggests pathogenic
brain-derived neurotrophic factor (BDNF), a member of the ne
and MD, the author suggests that BDNF could be a bridge be
symptoms in AD, and, cognitive impairment in MD. Evidence
antidepressants treatment for aged MD patients may decreas
central BDNF may offer an alternative treatment for MD patien
sufferers with depressive symptoms.

Cognitive Deficits in Chronic Stroke Patients: Neuropsychological Assessment, Depression, and Self-Reports

Arne E. Nakling[a, b] Dag Aarsland[b, c] Halvor Næss[a, d, e]
Daniel Wollschlaeger[f] Tormod Fladby[g, h] Håkon Hofstad[i] Eike Wehling[i]

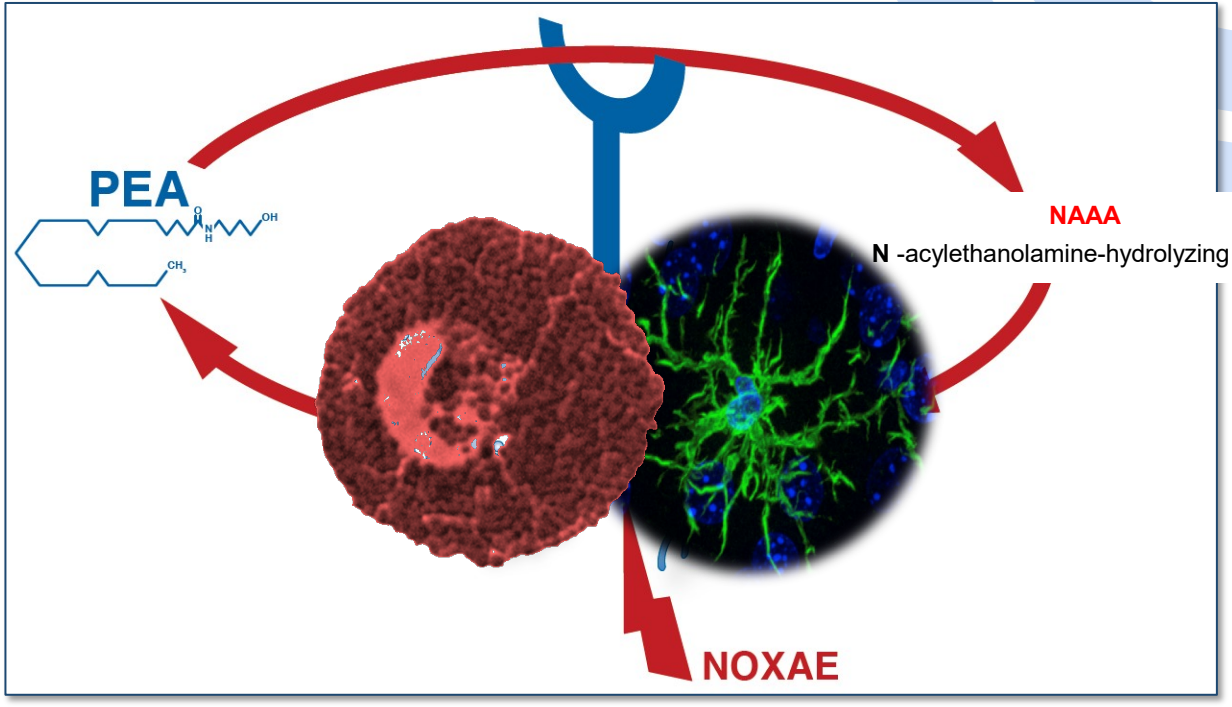
EXTRA Dementia and Geriatric Cognitive Disorders

Neuroinflammation drives anxiety and depression in relapsing-remitting multiple sclerosis

Neurology®

Silvia Rossi, MD*, Valeria Studer, MD*, Caterina Motta, MD, Serena Polidoro, MD, Jacopo Perugini, MD, Giulia Macchiarulo, MD, Ambra Mara Giovannetti, PsyD, Lorena Pareja-Gutierrez, RN, Andrea Calò, MD, Isabella Colonna, MD, Roberto Furlan, MD, Gianvito Martino, MD and Diego Centonze, MD

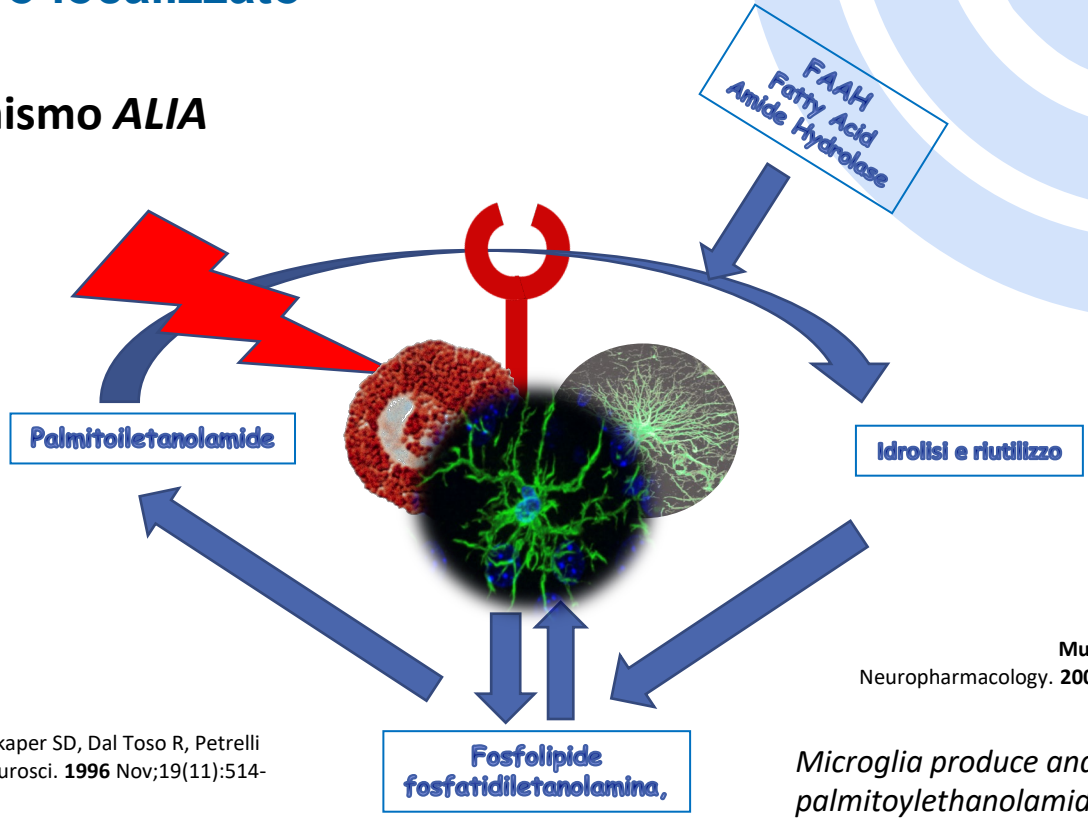
AUTACOID LOCAL INJURY ANTAGONISM



Contoso

STRATEGIE PER CONTRASTARE LA NEUROINFIAMMAZIONE
Il controllo delle cellule non neuronali e dello stress ossidativo localizzato

Il meccanismo *ALIA*



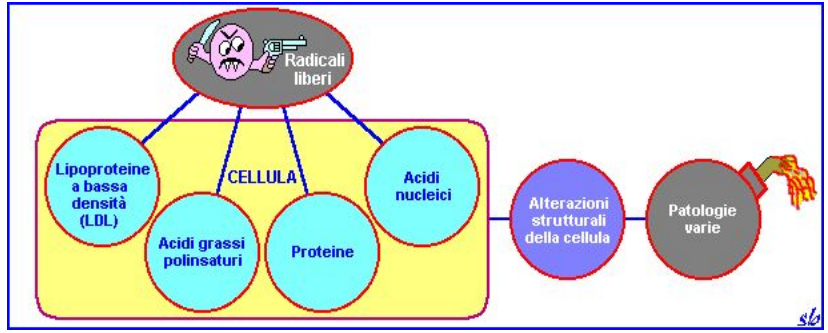
Muccioli GG, **Stella** N. Neuropharmacology. **2008** Jan;54(1):16-22.

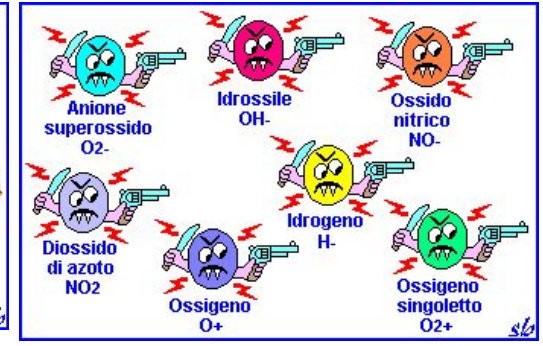
Microglia produce and hydrolyze palmitoylethanolamide

Levi-Montalcini R, Skaper SD, Dal Toso R, Petrelli L, Leon A. Trends Neurosci. **1996** Nov;19(11):514-20. Review.

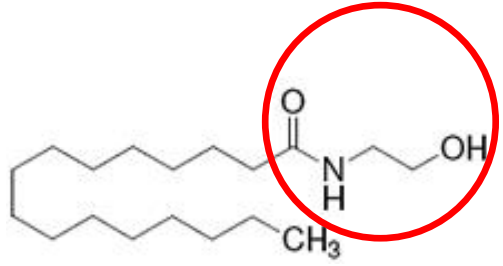
Contoso

Structural analogies with natural anti-oxidants

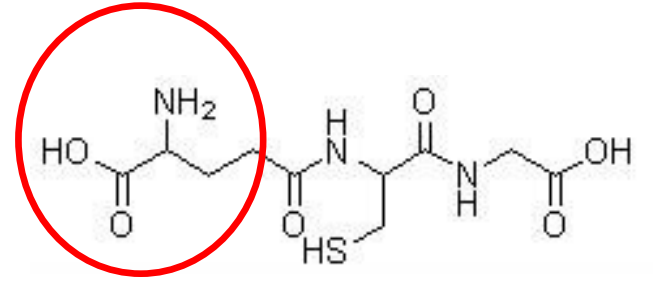




PEA



Glutatione



REA E LUTEOLINA

Exp Gerontol. 2017 Sep;95:39-43. doi: 10.1016/j.exger.2017.05.014. Epub 2017 May 17.

Luteolin as a potential preventive and therapeutic candidate for Alzheimer's disease.

Kwon Y[1].

⊕ Author information

Abstract

Amyloid cascade hypothesis is the main theoretical framework describing the development of Alzheimer's disease (AD). However, most clinical trials of therapy targeting amyloid-β peptide (Aβ) are unsuccessful because AD is a complex disease involving many genetic and environmental factors. Among various factors, inflammation within the brain in particular has been implicated in the pathogenesis and progression of AD. Furthermore, it has been shown that systemic inflammation can initiate AD. Therefore, anti-inflammatory agents might be beneficial for prevention and/or treatment of AD. Many reports have indicated that luteolin, a flavone found in various foods, has preventive and therapeutic value for neurodegenerative diseases including AD. Such effect of luteolin has been linked to its ability to relieve neuroinflammation. Luteolin also has other biological functions, including antioxidant activity that may provide added benefit for prevention of AD. The exact mechanisms of inflammatory pathways involved in AD pathogenesis need to be further understood to utilize luteolin and many other available anti-inflammatory agents to prevent and treat AD. In addition, it is critical to develop better experimental models that resemble the inflammatory conditions in clinical AD.

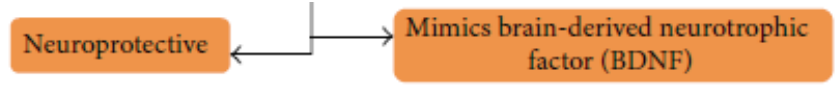


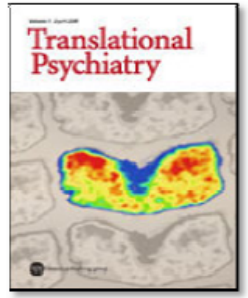
FIGURE 2: Luteolin (flavonoid) responsible for multiple biological functions.

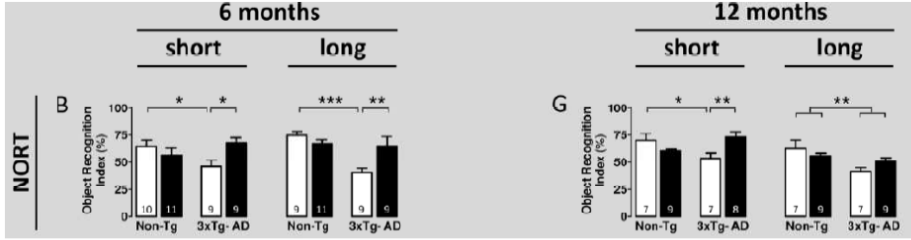
Contoso

Rasol et al., 2014

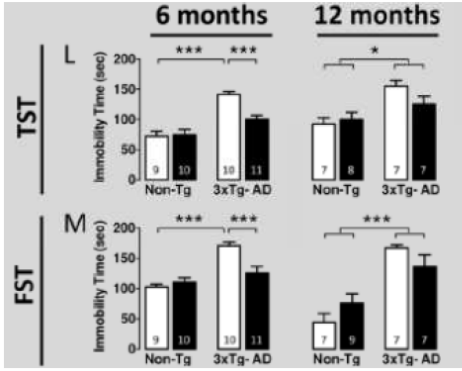
Ultramicronized palmitoylethanolamide rescues learning and memory impairments in a triple transgenic mouse model of Alzheimer's disease by exerting anti-inflammatory and neuroprotective effects

Caterina Scuderi[1], Maria Rosanna Bronzuoli[1], Roberta Facchinetti[1], Lorenzo Pace[2], Luca Ferraro[3], Kevin Donald Broad[4], Gaetano Serviddio[5], Francesco Bellanti[5], Gianmauro Palombelli[6], Giulia Carpinelli[6], Rossella Canese[6], Silvana Gaetani[1], Luca SteardoJr[7], Luca Steardo[1] and Tommaso Cassano[2]





Il trattamento con PEA-um ha migliorato l'apprendimento e la memoria degli animali con Alzheimer (test NORT).



NORT= è un test altamente validato per misurare la memoria nell'animale.

TST=metodica utilizzata per misurare lo stress nell'animale.

FST= è un test comportamentale fatto all'animale per valutare l'effetto antidepressivo di determinati principi attivi.

Placebo
um-PEA

Il trattamento con PEA-um ha migliorato inoltre i comportamenti depressivi negli animali con Alzheimer in fase intermedia (misurazione effettuata con TST e FST).

Scuderi et al, 2018

Contoso

outputs. Studies conducted in animal models of neurodegeneration indicate that PEA improves neurobehavioral functions, including memory and learning, by reducing oxidative stress and pro-inflammatory and astrocyte marker expression as well as rebalancing glutamatergic transmission. PEA was found to promote neurogenesis, especially in the hippocampus, neuronal viability and survival, and microtubule-associated protein 2 and brain-derived neurotrophic factor expression, while inhibiting mast cell infiltration/degranulation and astrocyte activation. It also demonstrated to mitigate β-amyloid-induced astrogliosis, by modulating lipid peroxidation, protein nytrosylation, inducible nitric oxide synthase induction, reactive oxygen species production, caspase3 activation, amyloidogenesis, and tau protein hyperphosphorylation. Such effects were related to PEA ability to indirectly activate cannabinoid receptors and modulate proliferator-activated receptor-α (PPAR-α) activity. Importantly,

Gabriella Gobbi*, Stefano Comai*,**,***

Review

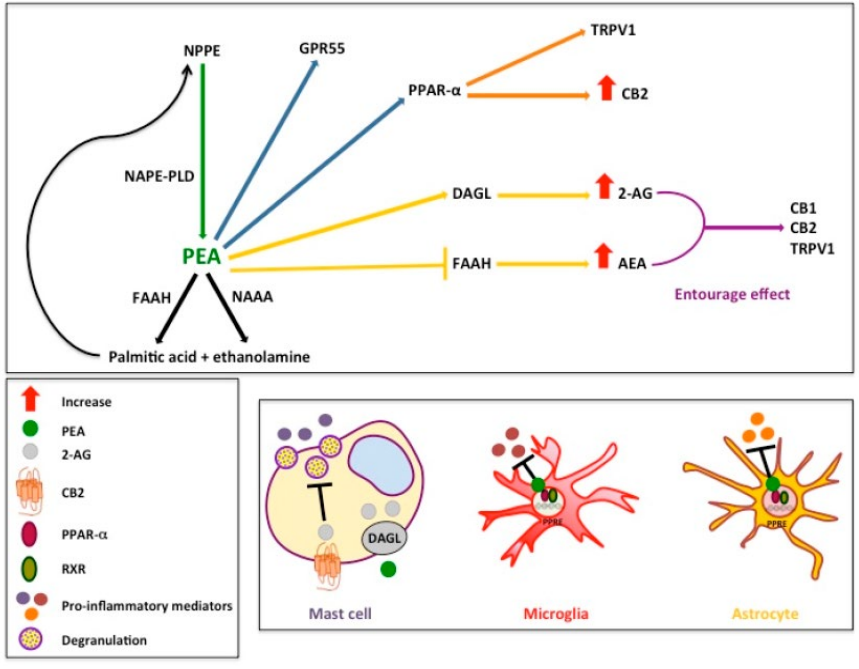
Palmitoylethanolamide: A Nutritional Approach to Keep Neuroinflammation within Physiological Boundaries. A Systematic Review

Stefania Petrosino [1,2,*] and Aniello Schiano Moriello [1,2]

2020

International Journal of *Molecular Sciences*

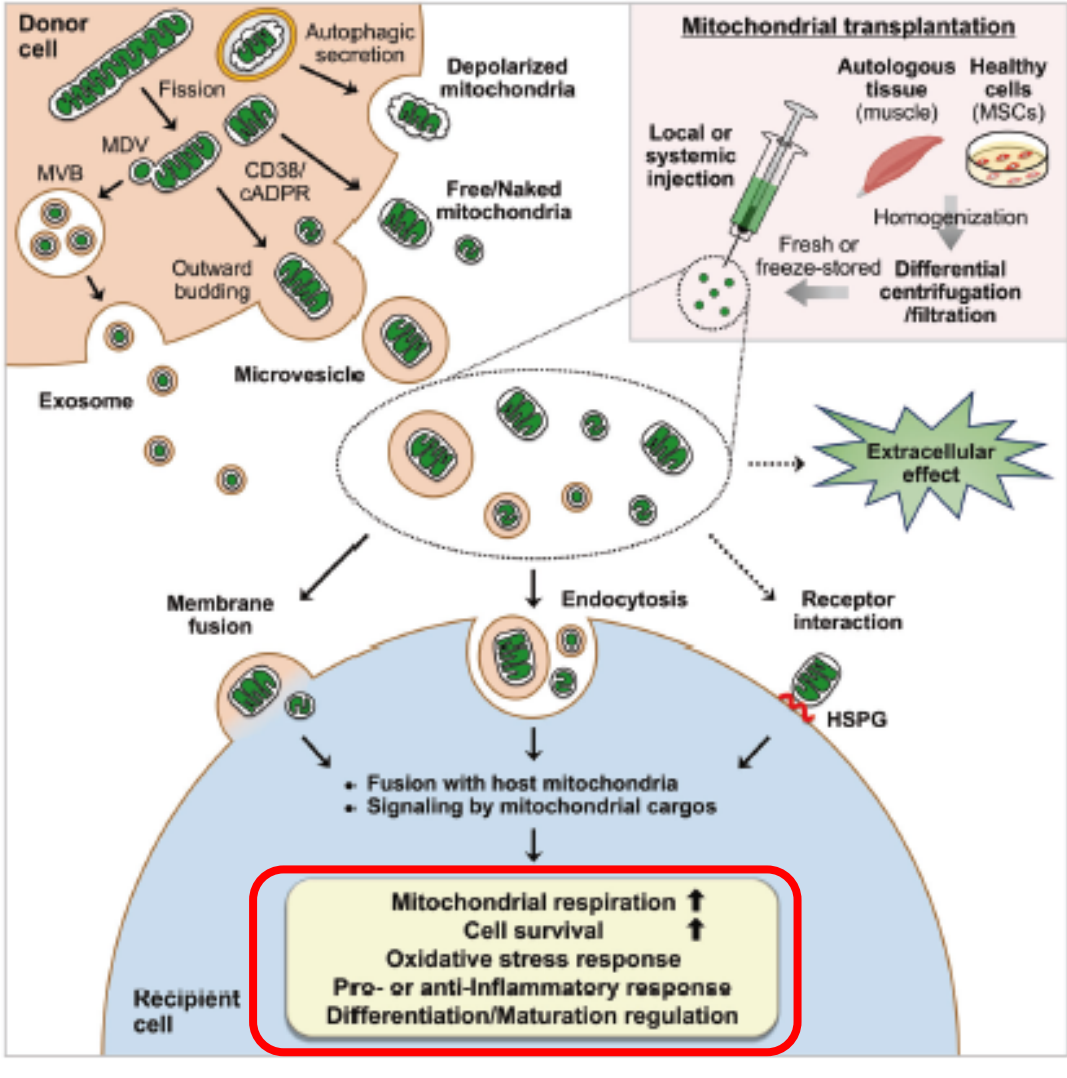
PALMITOILETANOLAMIDE



PEA-um agisce da modulatore pro-omeostatico delle cellule non neuronali distribuite nei tessuti periferici e centrali (Meccanismo ALIA).

PEA-um attiva vari recettori (es. PPAR-α, GPR55) espressi nel nucleo e sulle membrane delle cellule non neuronali, inducendo un profondo effetto anti-neuroinfiammatorio e neuroprotettore.

PEA-um potenzia l'attività del sistema endocannabinoide (2-AG, AEA), anch'esso implicato nella risposta antinfiammatoria e neuroprotettiva.



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REVIEW ARTICLE OPEN

Check for updates

Mitochondria as secretory organelles and therapeutic cargos

Joonho Suh[1] and Yun-Sil Lee[1]✉

Experimental & Molecular Medicine; https://doi.org/10.1038/s12276-023-01141-7

SUBSTANCES THAT INHIBIT MICROGLIAL ACTIVATION AND NEUROINFLAMMATION ARE PROTECTIVE IN NEURODEGENERATIVE DISEASES

- Resveratrol - In PD resveratrol participation is still being studied, but it seems to have a protective effect against dopamine-induced cytotoxicity and certain toxins and can also attenuate the inflammatory response in activated microglia

- Curcumin – phenolic compound extracted from perennial herb *Curcuma longa* (turmeric), characterized for its anti-inflammatory and antioxidant properties. Among its properties, curcumin inhibits microglial proliferation and differentiation and reduces the inflammation

- Riluzole - In PD, Riluzole has shown neuroprotective properties reducing GFAP levels in the lesioned striatum in a rodent model

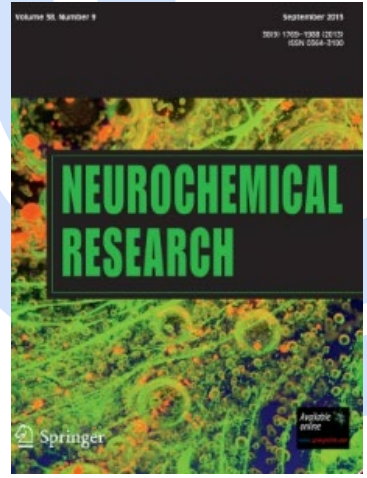
Review > Neurochem Res. 2018 Sep;43(9):1705-1713. doi: 10.1007/s11064-018-2586-8. Epub 2018 Jun 25.

Resveratrol Boosts Cognitive Function by Targeting SIRT1

Wenyan Cao [1], Ying Dou [1], Aiping Li [2]

Affiliations + expand

PMID: 29943083 DOI: 10.1007/s11064-018-2586-8

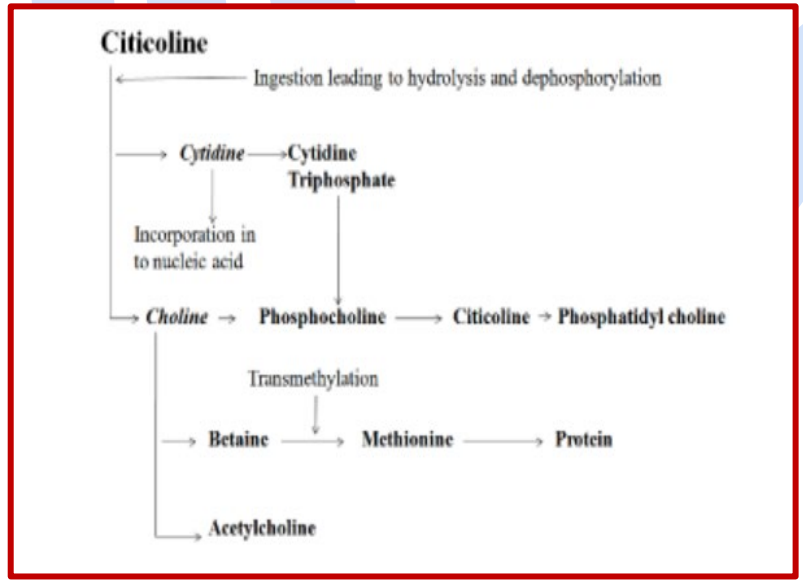


Resveratrol's antioxidant effect promotes neuronal development by activating the silent information regulator-1 (SIRT1), which can protect against the detrimental effects of oxidative stress. Resveratrol-induced SIRT1 activation is becoming more crucial in developing novel therapeutic options for AD and other diseases that have neurodegenerative characteristics.

Contoso

COLINA E NEUROPROTEZIONE

- Choline and the choline-containing phospholipid phosphatidylcholine are essential for maintaining cell membrane integrity and structure.
- Activates the biosynthesis of structural phospholipids in the neuronal membranes
- Increases cerebral metabolism
- Increases noradrenaline and dopamine levels in the CNS
- Has a neuroprotective effect during hypoxia and ischemia (vascular cognitive impairment)



Fosfolipidi contenenti colina

- *Fosfatidilcolina*
- *Gliceril fosforilcolina (colina alfoscerato)*
- *Citidilfosforilcolina (CDP-Colina o Citicolina)*
- *Sfingosil fosforilcolina*
- *Lisofosfatidilcolina*

POTENZIALI CANDIDATI PER UN RUOLO DI NEUROPROTEZIONE?

Review > Pharmacol Res. 2022 Dec:186:106550. doi: 10.1016/j.phrs.2022.106550.
Epub 2022 Nov 11.

Glucagon-like peptide-1 (GLP-1) receptor agonists and neuroinflammation: Implications for neurodegenerative disease treatment

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Affiliations + expand

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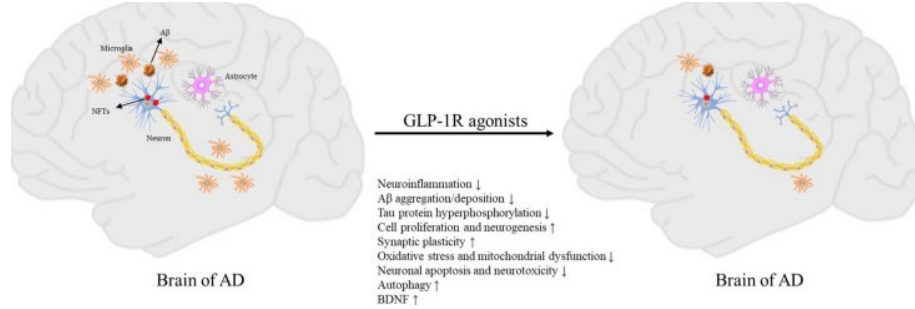

A livello dell'encefalo il GLP-1 è prodotto da alcuni neuroni del tronco encefalico, in particolare dal nucleo del tratto solitario, e dalla microglia M2

Il GLP-1 viene ampiamente distribuito a molteplici recettori del GLP-1 (GLP-1Rs) presenti nel SNC, su astrociti e microglia, ma viene anche impiegato come neurotrasmettitore

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Glucagon-like peptide-1 class drugs show clear protective effects in Parkinson's and Alzheimer's disease clinical trials: A revolution in the making?

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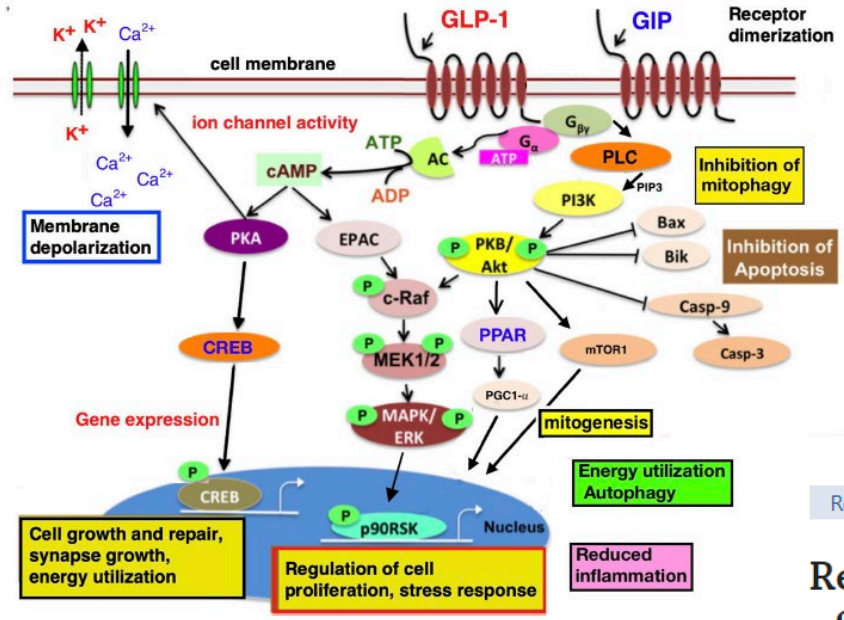

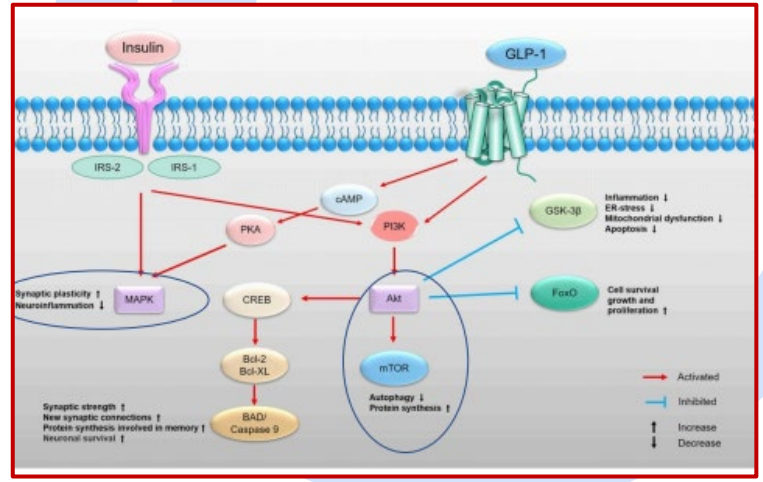

La stimolazione dei GLP-1Rs porta all'attivazione di due importanti vie di segnale: quella del MAPK e quella di Akt/mTOR

Ne consegue l'attivazione di sintesi proteica, proliferazione cellulare e biogenesi mitocondriale e l'inibizione di apoptosi, infiammazione e aggregazione di prodotti proteici

Review › Endocr Rev. 2021 Mar 15;42(2):101-132. doi: 10.1210/endrev/bnaa032.

Revisiting the Complexity of GLP-1 Action from Sites of Synthesis to Receptor Activation

Conclusioni (1)

- Le cellule gliali e microgliali rappresentano i nuovi target per il trattamento delle patologie caratterizzate dalla neuroinfiammazione

- L'identificazione di nuovi target molecolari sulle cellule non neuronali può rappresentare una nuova possibilità di intervento terapeutico nell'inflammaging accelerato

- Evidenze genetiche dimostrano che alterazioni del recettore TREM 2 con conseguente disfunzione dell'attività delle cellule della microglia possono contribuire alla progressione della neurodegenerazione

- Evidenze su modelli animali dimostrano una complessa alterazione del funzionamento dell'unità neurovascolare, in particolare dell'interazione tra cellule della microglia, astrociti e neuroni che favoriscono l'inflammaging

- Danno vascolare, lesione neuronale e/o neurodegenerazione e neuroinflammaging costituiscono una comune triade patologica che si verifica in molteplici disturbi neurologici

Conclusioni (2)

- Ruolo in prevenzione primaria di: alimentazione corretta, attività fisica, controllo di eventuale disbiosi intestinale, obesità, e soprattutto lo stress cronico
- E' concepibile che gli agenti "multi-bersaglio, multi-azione" avranno maggiori possibilità di controllare i complessi meccanismi della malattia che mediano la neurodegenerazione rispetto agli agenti che hanno un solo bersaglio (ad esempio, i neuroni)
- L'utilizzo di molecole endogene (PEA) con attività immunomodulante (linfociti, macrofagi, mastociti, microglia) può rappresentare una strategia terapeutica alternativa per le patologie neurodegenerative associate a neuro-immuno-infiammazione accelerata
- Parimenti, l'utilizzo di sostanze capaci di attivare la sirtuina-1 (citicolina) è un altro modo esplicito di attivare la neurotrasmissione colinergica ed esercitare effetti antiossidanti e contrastanti l'azione neurotossica del glutammato

IL MEDICO = lavorare con le proprie EMOZIONI, coltivare la propria PASSIONE e la SCIENZA della professione, sapendo di NON sapere

GRAZIE PER L' ATTENZIONE