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PALAZZO DEI CONGRESSI

Biomarcatori di fragilità fisica e cognitiva

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Fragilità

- ✓ La fragilità è una sindrome molto frequente nelle persone anziane
- ✓ Caratterizzata da una aumentata vulnerabilità agli stress, sia endogeni che esogeni, e da una ridotta riserva omeostatica
- ✓ Da un punto di vista biologico, la fragilità è determinata dall'accumulo graduale, di alterazioni a livello molecolare e cellulare che coinvolgono diversi organi e sistemi
- ✓ Per questo motivo è indice dell'età biologica dell'individuo
- ✓ Esistono molteplici definizioni per quantificare la fragilità e molti approcci operativi sono stati proposti nel tempo
- ✓ Gli strumenti operativi si basano prevalentemente su due modelli: l'indice di fragilità (FI) e il fenotipo di fragilità (FP)

Fragilità

Inoltre:

“physical frailty and sarcopenia” in cui la sarcopenia viene considerata il substrato biologico della fragilità fisica (Landi F. et al. 2015)

“cognitive frailty” è stata introdotta per spiegare gli esiti avversi comunemente osservati nelle persone in cui coesistono fragilità e deficit cognitivi (Kelaiditi E. et al. 2013)

Tuttavia:

i meccanismi biologici che identificano fragilità fisica e fragilità cognitiva sono ancora da caratterizzare…

Cosa è un biomarcatore

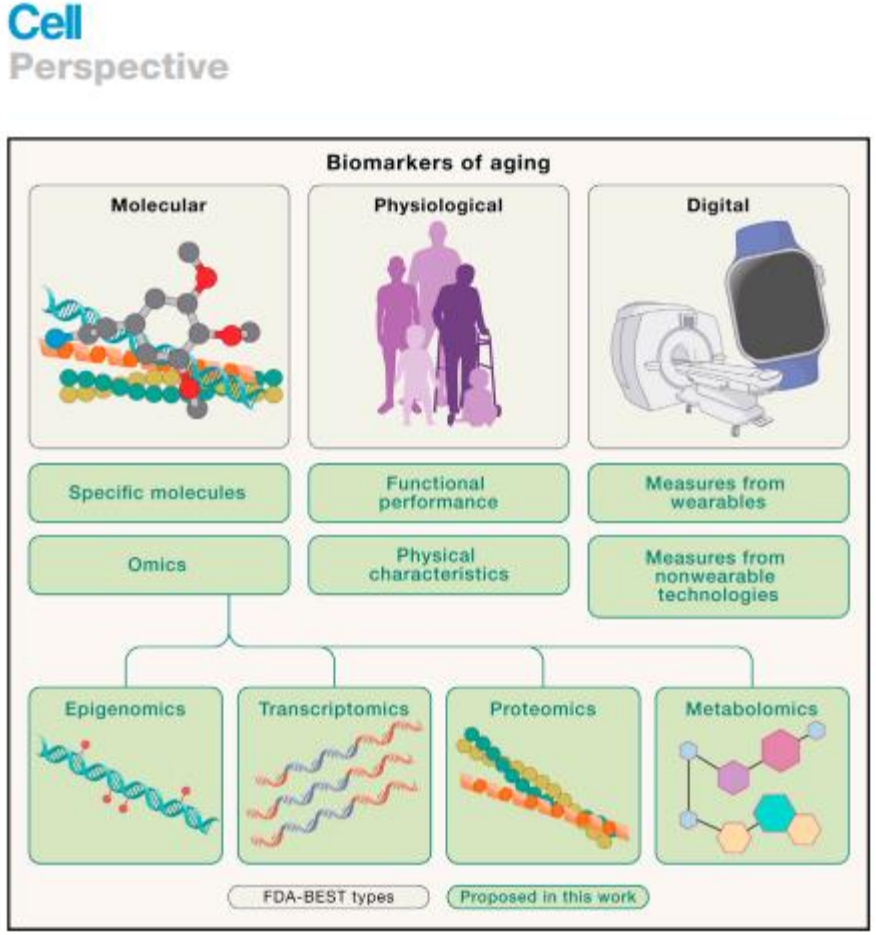
Box 1: National Institutes of Health (NIH) Definition Working Group definitions for biomarkers and clinical end points (modified by NIH[1] and Vassan[4])

- **Biomarker**: a characteristic objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention.
  - **Type 0 biomarker**: a marker of the natural history of a disease that correlates longitudinally with known clinical indices.
  - **Type I biomarker**: a marker that captures the effects of a therapeutic intervention in accordance with its mechanism of action.
- **Clinical end point**: a characteristic or variable that reflects how a patient feels, functions or survives.
  - **Intermediate (non-ultimate) end point**: a true clinical end point (a symptom or measure of function, such as symptoms of angina frequency or exercise tolerance), but not the ultimate end point of the disease.
  - **Ultimate end point**: eg, survival or the rate of other serious and irreversible morbid events.
- **Surrogate end point**: a biomarker intended to substitute for a clinical end point aiming to predict clinical benefit (or harm, or lack of benefit or harm) on the basis of epidemiological, therapeutic, pathophysiological or other scientific evidence.

Postgrad Med J 2009;**85**:538–545. doi:10.1136/pgmj.2008.073759

Box 2: Multiple roles of biomarkers

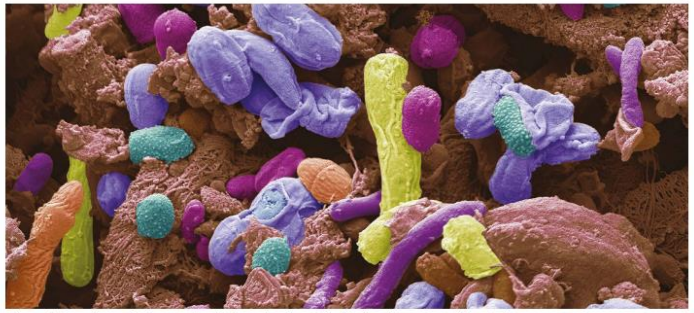
- Antecedent: identifying the risk of developing an illness
- Screening: screening for subclinical disease
- Diagnostic: recognising overt disease
- Staging: categorising disease severity
- Prognostic: predicting future disease course/response to therapy



Moqri M. et al. 2023

Biomarcatori di fragilità fisica e cognitiva

The international journal of science / 9 November 2023
nature



Changes in the make-up of microorganisms in the gut have been linked to disorders such as Parkinson's disease.

Brain and body are more intertwined than we knew

A host of disorders once thought to be nothing to do with the brain are, in fact, tightly coupled to nervous-system activity.

For decades, scientists thought of the brain as the body's most valuable – and consequently most closely guarded – asset. Locked safely behind a biological barrier, away from the hurly-burly of the rest of the body, it was broadly free of the ravages of invading germs, the battles waged by the immune system and the constant churn of cells.

Then, 20-odd years ago, some researchers began to ask a heretical question: is the brain really so isolated? The answer, according to a growing body of evidence, is no – and has important implications for both science and health care.

The list of brain conditions that have been associated with changes elsewhere in the body is long and growing. Changes in the make-up of the microorganisms resident in the gut, for example, have been linked to disorders such as Parkinson's disease and motor neuron disease. Some researchers think that certain infections could provoke the onset of Alzheimer's disease; there is also a theory that infection during pregnancy could lead to autism spectrum disorder in babies.

> "If some brain conditions start outside the brain, then perhaps therapies could also reach in from outside."

The effect is two-way. There is a lengthening list of symptoms not typically viewed as disorders of the nervous system in which the brain and the neural processes that connect it to the body play a large part. For example, the development of a fever is influenced by a population of neurons that control body temperature and appetite. The effect of brain on body is underlined by the finding that stimulating a particular brain region in mice can 'remind' the body of previous bouts of inflammation – and reproduce them[1].

The list goes on. Evidence is mounting that cancers use nerves to grow and spread. In this week's *Nature*, Michelle Monje and her colleagues[2] show how some brain cancers consolidate connections with neurons that enhance their progression (see page 366). Meanwhile, Jonathan Lovelace and his colleagues[3] explore the neural pathway that can cause a drop in blood pressure and fainting (see page 387). This comprises a group of nerves that project from the heart to the brainstem.

These findings and others mark a radical shift in our view of the nervous system, and neuroscientists are still only beginning to explore its impacts. To really get to grips with how the brain and the body are entangled, researchers in a range of fields will need to work together more closely. Ultimately, the goal should be to study the interplay between the brain and body in humans. This will require methods for accessing brain function, such as functional magnetic resonance imaging, as Emily Finn and her colleagues[4] describe in a Perspective article (see page 263).

The interconnectedness of brain and body has tantalizing implications for our ability to both understand and treat illness. If some brain conditions start outside the brain, then perhaps therapies for them could also reach in from outside. Treatments that take effect through the digestive system, heart or other organs, for instance, would

nutrients
MDPI

Review

Sarcopenia and Cognitive Decline in Older Adults: Targeting the Muscle–Brain Axis

Beatrice Arosio [1], Riccardo Calvani [2,3], Evelyn Ferri [4], Hélio José Coelho-Junior [3], Angelica Carandina [1], Federica Campanelli [5], Veronica Ghiglieri [2,6], Emanuele Marzetti [2,3,*] and Anna Picca [2,7]

Arosio B. et al. 2022

Muscle-brain axis?

Gamberale et al. BMC Geriatr (2021) 21:633
https://doi.org/10.1186/s12877-021-02584-1

BMC Geriatrics

STUDY PROTOCOL Open Access

Study protocol: understanding the pathophysiologic mechanisms underlying delirium in older people undergoing hip fracture surgery

R. Gamberale[1], C. D'Orlando[1], S. Brunelli[1], R. Meneveri[1], P. Mazzola[1,2], G. Foti[1,2], G. Bellani[1,2], G. Zatti[2], D. Munegato[2], S. Volpato[3], A. Zurlo[4], G. Caruso[5], A. Andreano[1], M. G. Valsecchi[1] and G. Bellelli[1,2*]

Table 2 Selected biomarkers for the study

Biomarkers	Blood (plasma)	Blood (PBMCs)	Cerebrospinal fluid	Muscle
Pro-inflammatory cytokines	IL-6 [S1, S2, S3] IL-8 [S1, S2, S3] IL-1β [S1, S2, S3] TNF-α [S1, S2, S3] IFNγ [S1, S2, S3]	IL-6 [S1, S2, S3] IL-8 [S1, S2, S3] IL-1β [S1, S2, S3] TNF-α [S1, S2, S3] IFNγ [S1, S2, S3]	IL-6 [S1, S2, S3] IL-8 [S1, S2, S3] IL-1β [S1, S2, S3] TNF-α [S1, S2, S3] IFNγ [S1, S2, S3]	IL-6 [S1, S2, S3] IL-8 [S1, S2, S3] IL-1β [S1, S2, S3] TNF-α [S1, S2, S3] IFNγ [S1, S2, S3]
Anti-inflammatory cytokines	IL-10 [S1, S2, S3] IL-37 [S4] TGF-β [S3]	IL-10 [S1, S2, S3] IL-37 [S4] TGF-β [S3]	IL-10 [S1, S2, S3] IL-37 [S4] TGF-β [S3]	IL-10 [S1, S2, S3] IL-37 [S4] TGF-β [S3]
Muscular damage and regeneration				Atrogin-1 [S5] MuRF-1 [S5] Myostatin [S5] Follistatin [S5] Activin [S5] Activin receptor type II [S5] Myosin heavy chain type II [S5] Myosin heavy chain type VII [S5]
Muscle differentiation				PAX7 [S5] MyoD [S5] Myogenin [S5] MYF5 [S5] MEF2A [S5]
Endothelial damage	CD-31 [S6] S-100β [S3, S7] Von Willebrand factor [S6]	CD-31 [S6] S-100β [S3, S7] Von Willebrand factor [S6]	CD-31 [S6] S-100β [S3, S7] Von Willebrand factor [S6]	
Transport proteins	Albumin [S1, S2]	Albumin [S1, S2]	Albumin [S1, S2]	
Immune system activation	Neopterin [S8]	Neopterin [S8]	Neopterin [S8]	
Neurodegeneration	Neurofilament light chain [S9]	Neurofilament light chain [S9]	Neurofilament light chain [S9]	
Stress response	Cortisol [S10, S11]		Cortisol [S10, S11]	

Biomarkers coming from fluids (plasma and CSF) will be measured by protein quantification assays, while biomarkers coming from cells (PBMCs and myocytes) will be measured by mRNA expression analysis

Concentrazioni plasmatiche pre-operatorie

	DEL- (n 46)	DEL+ (n 11)	*P*
IFN γ (pg/mL)	0,37 (0,16-0,66)	0,26 (0,10-1,16)	0,54
IL-10 (pg/mL)	4,68 (3,30-7,48)	7,72 (2,58-10,20)	0,58
IL-6 (pg/mL)	38,95 (22,08-50,00)	38,60 (20,80-71,10)	0,94
TNF α (pg/mL)	11,50 (8,21-15,90)	14,30 (9,37-17,10)	0,49
BDNF (ng/mL)	1,72 (0,98-0,13)	2,99 (1,03-5,84)	0,25
IL-1β (pg/mL)	0,12 (0,00-0,41)	0,06 (0,00-0,33)	0,67
TNFR1 (ng/mL)	2,03 (1,54-2,55)	2,28 (1,87-2,78)	0,41
TREM1 (pg/mL)	656 (460-910)	699 (539-958)	0,59
TREM2 (ng/mL)	29,32 (24,23-37,30)	37,68 (30,44-63,26)	0,06
NfL (pg/mL)	**40,65 (27,33-69,98)**	**57,40 (51,30-109,00)**	**0,01**
IL-1ra (pg/mL)	531 (380-980)	748 (576-1113)	0,33
IL-8 (pg/mL)	8,14 (5,94-12,60)	8,29 (5,98-15,30)	0,74
Irisina (ng/mL)	55,54 (39,80-100,54)	60,50 (19,25-101,05)	0,73

I valori sono espressi come mediana (intervallo interquartile)

Variazione delle concentrazioni plasmatiche (delta T1-T0)

	DEM- DEL- (n 46)	DEM- DEL+ (n 11)	*p*
IFN γ (pg/mL)	0,03 (-0,34-0,22)	-0,08 (-0,30-0,13)	0,35
IL-10 (pg/mL)	1,15 (-1,47-3,92)	2,42 (-2,61-5,82)	0,75
IL-6 (pg/mL)	40,20 (1,34-78,52)	73,80 (6,00-99,80)	0,38
TNF α (pg/mL)	0,63 (-2,46-4,75)	-0,06 (-3,80-1,30)	0,41
BDNF (ng/mL)	**0,29 (-0,41-2,20)**	**-0,72 (-4,02-(-0,03))**	**0,01**
IL-1β (pg/mL)	0,00 (-0,14-0,14)	0,04 (0,00-0,10)	0,32
TNFR1 (ng/mL)	0,32 (-0,19-0,69)	0,24 (-0,11-1,13)	0,56
TREM1 (pg/mL)	8,59 (138,65)	26,91 (216,67)	0,73
TREM2 (ng/mL)	**-1,11 (-6,05-5,37)**	**-6,21 (-15,83-(2,63))**	**0,02**
NfL (pg/mL)	12,90 (2,82-20,95)	3,20 (-11,10-22,40)	0,13
IL-1ra (pg/mL)	594 (271-1703)	514 (57,00-924)	0,41
IL-8 (pg/mL)	3,87 (1,13-7,82)	4,81 (0,54-6,86)	0,84
Irisina (ng/mL)	37,65 (9,89-52,75)	12,90 (-18,50-50,00)	0,35

I valori sono espressi come mediana (intervallo interquartile)

Concentrazione preoperatoria e rischio di delirium

	OR (CI)	*p*
BDNF	1,53 (0,40-5,80)	0,53
IL-1β	0,39 (0,10-1,57)	0,18
NfL	**4,61 (1,00-21,26)**	**0,05**

Variazione perioperatoria e rischio di delirium

	OR (CI)	*p*
BDNF	**0,16 (0,03-0,88)**	**0,03**
TREM2	**0,18 (0,04-0,83)**	**0,03**
Irisina	0,65 (0,14-3,01)	0,59

✓**BDNF: la concentrazione peri-operatoria di BDNF aumenta del 31% in coloro che non sviluppano delirium e si riduce invece del 55% in coloro che lo sviluppano. La regressione logistica conferma che una riduzione di BDNF peri-operatoria aumenta il rischio di delirium**

✓**TREM-2: la concentrazione peri-operatoria di TREM2 si riduce maggiormente in coloro che sviluppano delirium (riduzione del 5%). La regressione logistica conferma che una riduzione di TREM2 peri-operatoria aumenta il rischio di delirium**

✓**NfL: la concentrazione preoperatiria di NfL è più alta in quelli che sviluppano delirium. La regressione logistica conferma che alti livelli al basale aumentano il rischio di delirium**

Neurofilament light

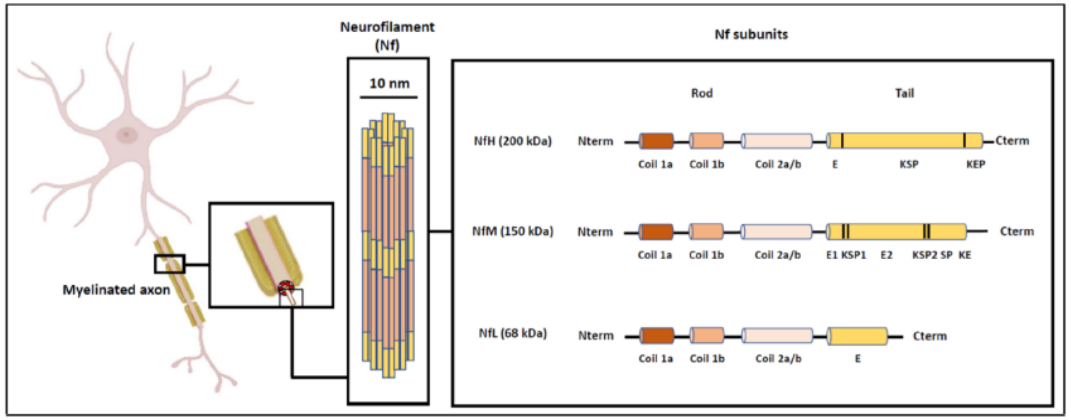


FIGURE 1
Structure and organization of neurofilaments (Nf), adapted from Gaetani et al. (2019).

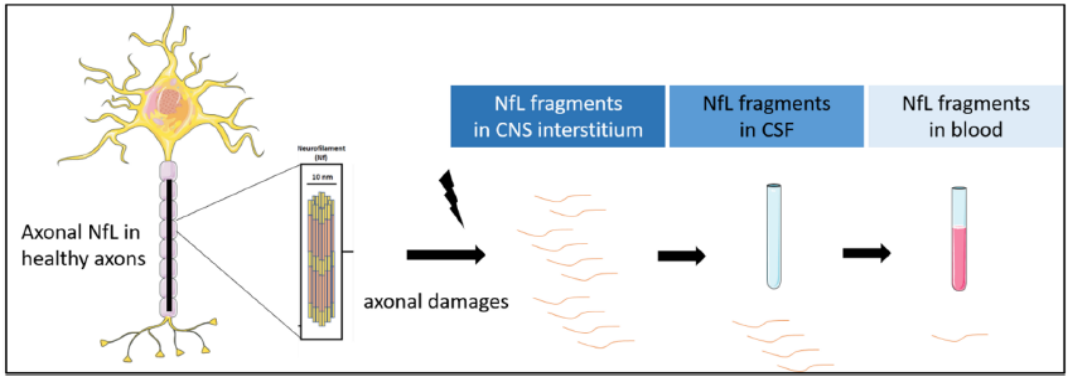
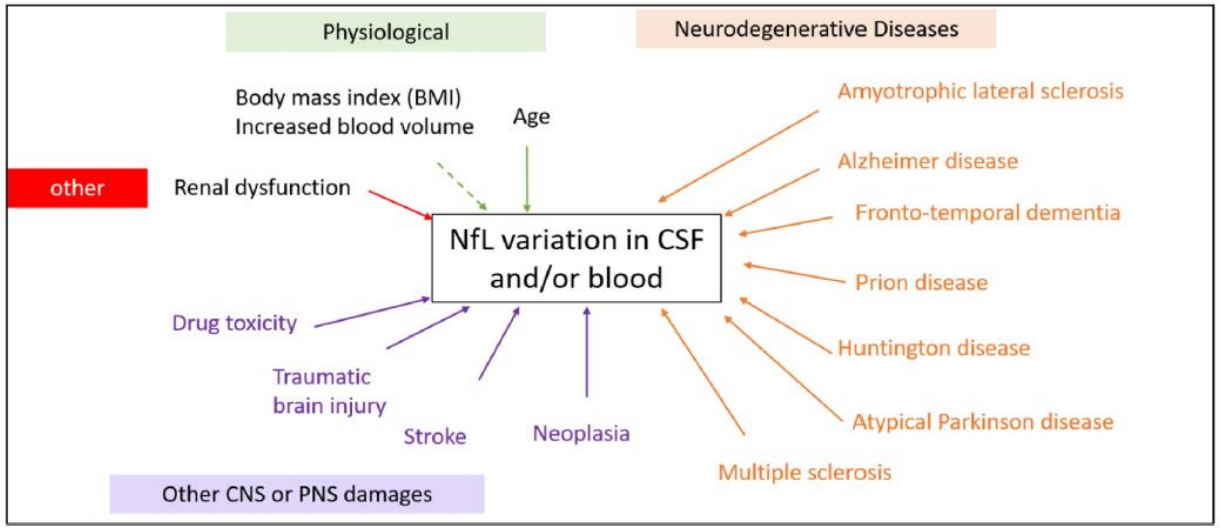


FIGURE 2
NfL release after axonal damages. NfL are detectable in CSF and blood.



Delabi C. et al. 2022

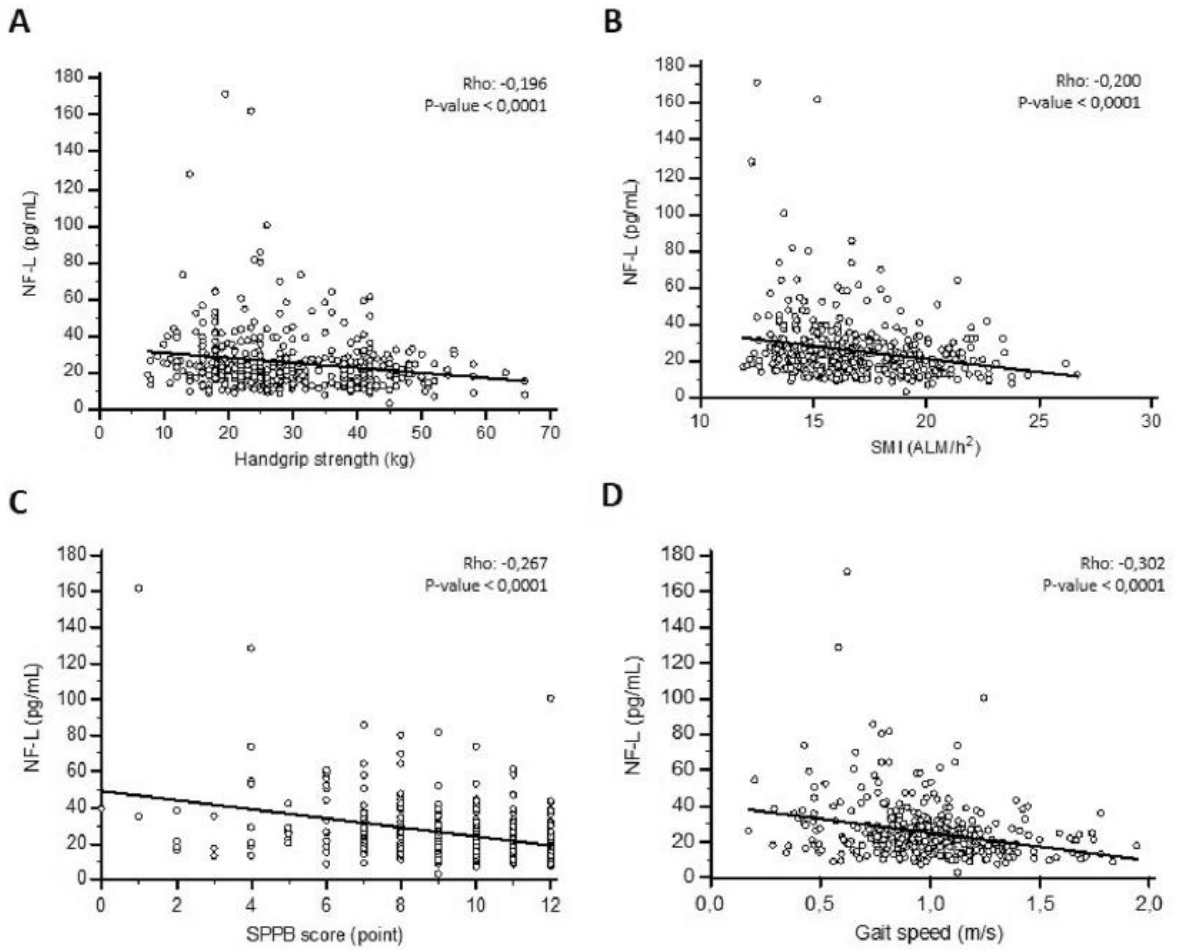
Aging Clinical and Experimental Research
https://doi.org/10.1007/s40520-023-02521-9

ORIGINAL ARTICLE

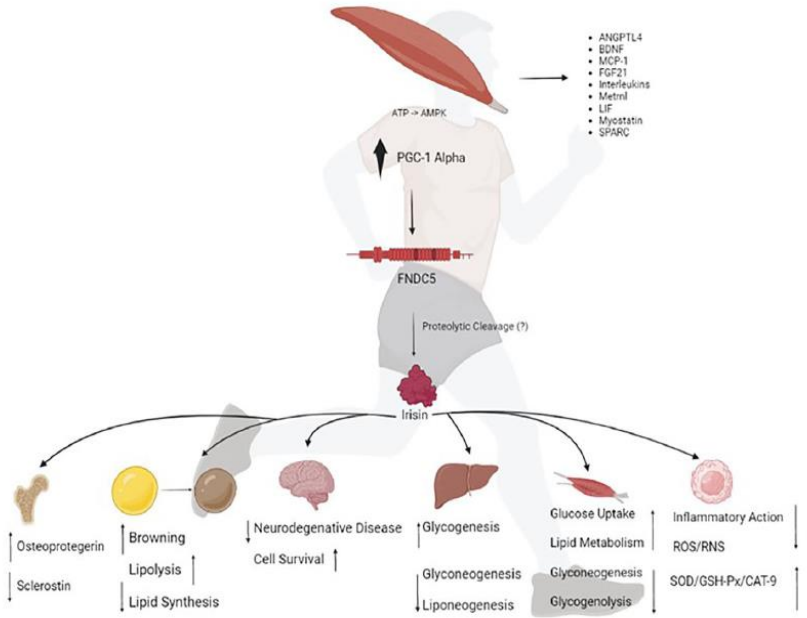
Neurofilament-light chains (NF-L), a biomarker of neuronal damage, is increased in patients with severe sarcopenia: results of the SarcoPhAge study

Aurélie Ladang[1] · Stéphanie Kovacs[1] · Laetitia Lengelé[2] · Médéa Locquet[2] · Charlotte Beaudart[2] · Jean-Yves Reginster[2] · Olivier Bruyère[2,3] · Etienne Cavalier[1]

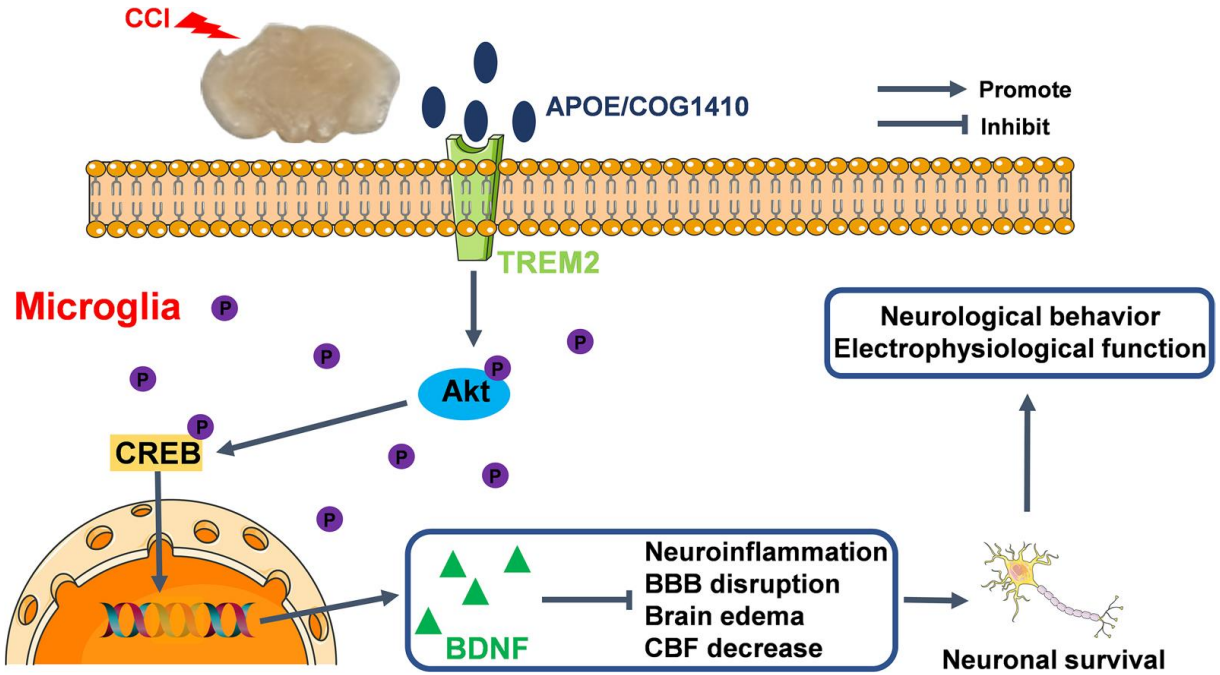
Received: 13 June 2023 / Accepted: 27 July 2023



Brain-derived neurotrophic factor (BDNF) e Triggering receptor expressed on myeloid cells (TREM2)

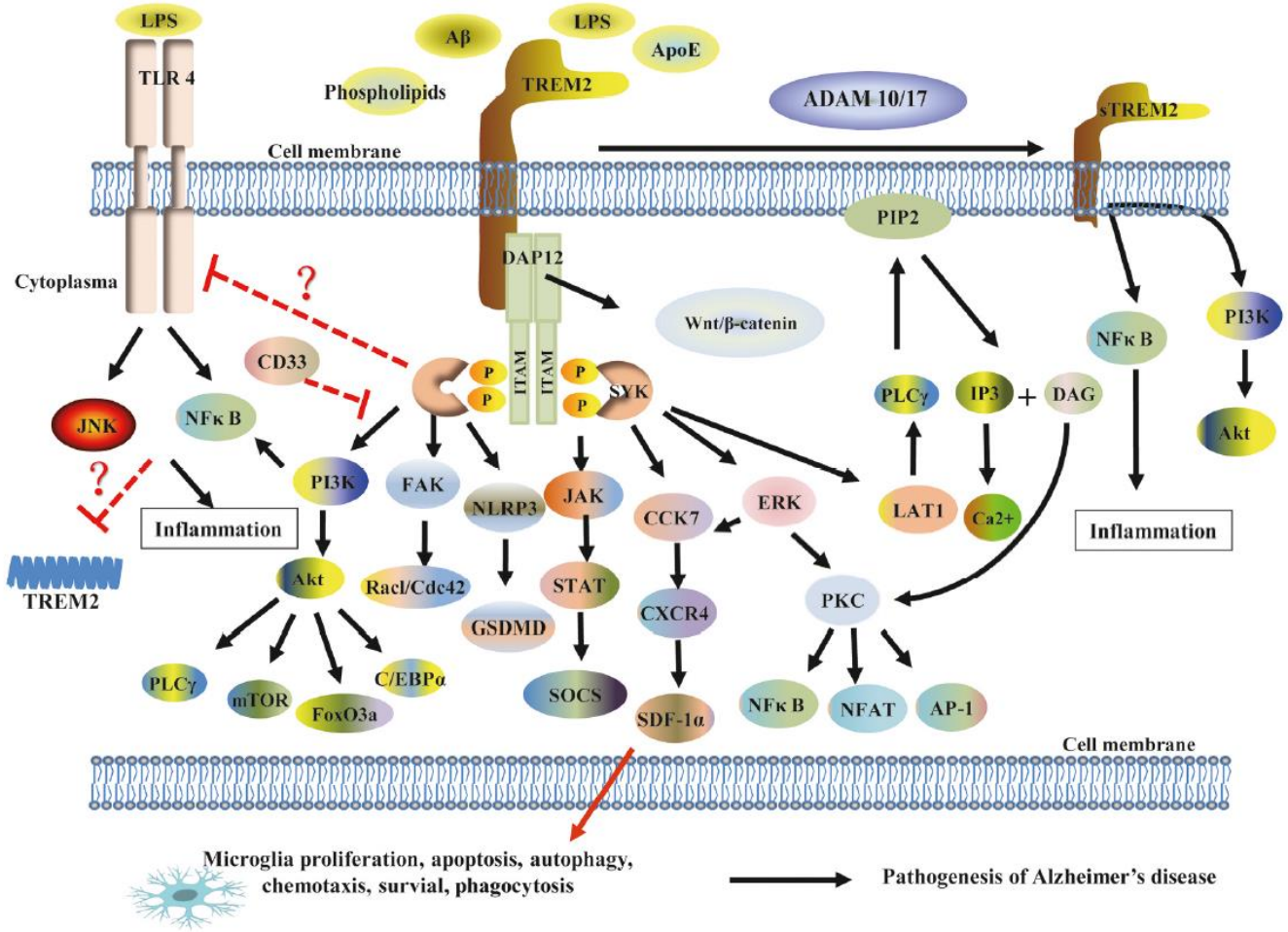


Trettel CdS. et al. 2023



Yan J et al. 2022

Triggering receptor expressed on myeloid cells 2



Li Y. et al. 2023