CORSO EDUCAZIONALE

GRUPPO LINFOMI IN PAZIENTI CON IMMUNODEFICIT

Milano, UNAHOTELS Galles

23 maggio 2025

Come valutare l'inflammaging nella patogenesi dei linfomi e nella malattia di Castleman

Lara Gibellini

Nothing to disclose

Outline

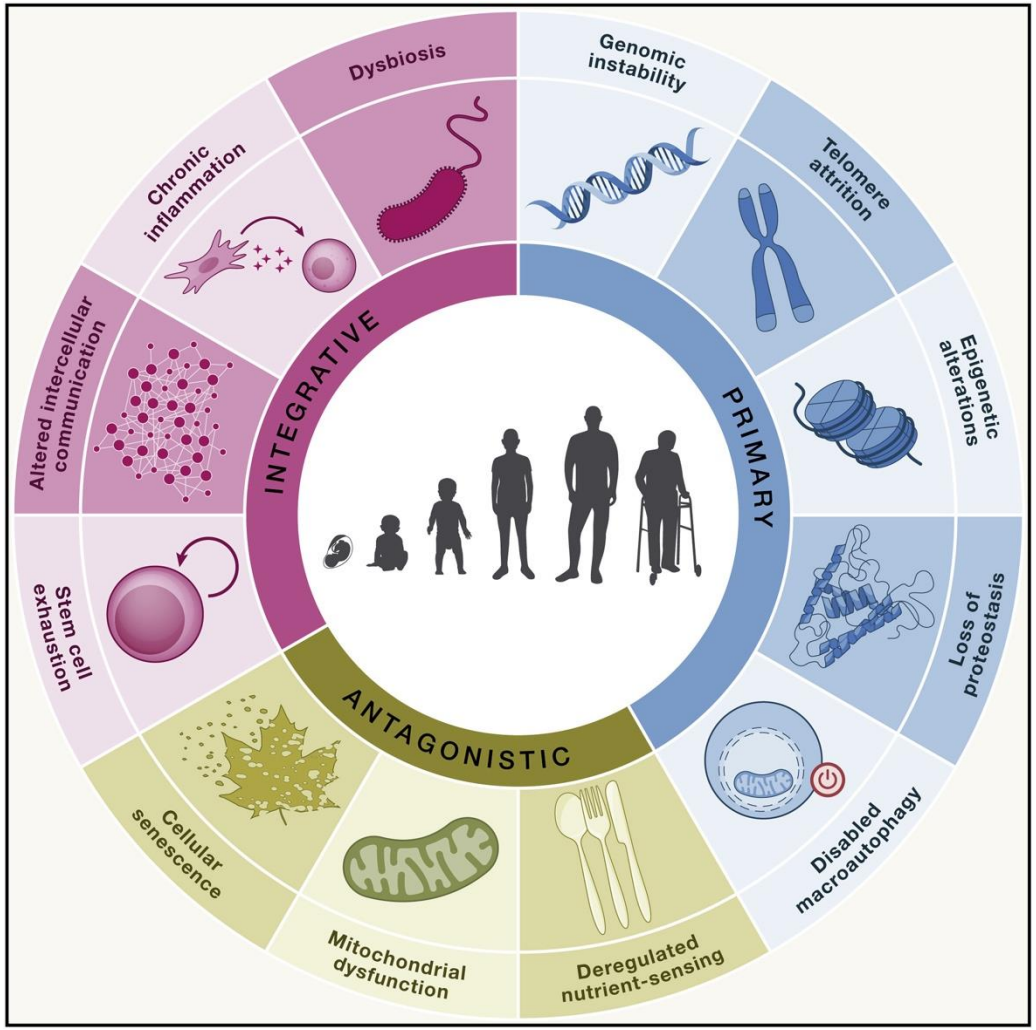
- Definition of inflammaging
- Possible causes
- Possible consequences
- How to measure inflammaging
- Considerations on lymphoma and Castleman Disease

Persistent chronic inflammation: inflammaging

- **Low-grade, chronic state of inflammation**
- **Increased levels of IL-6, CRP, fibrinogen, IL-1β, TNF among others**

- Still unknown whether inflammaging, which represents a risk factor for most age-related pathologies, is the cause or rather the effect of the aging process.

The hallmarks of aging

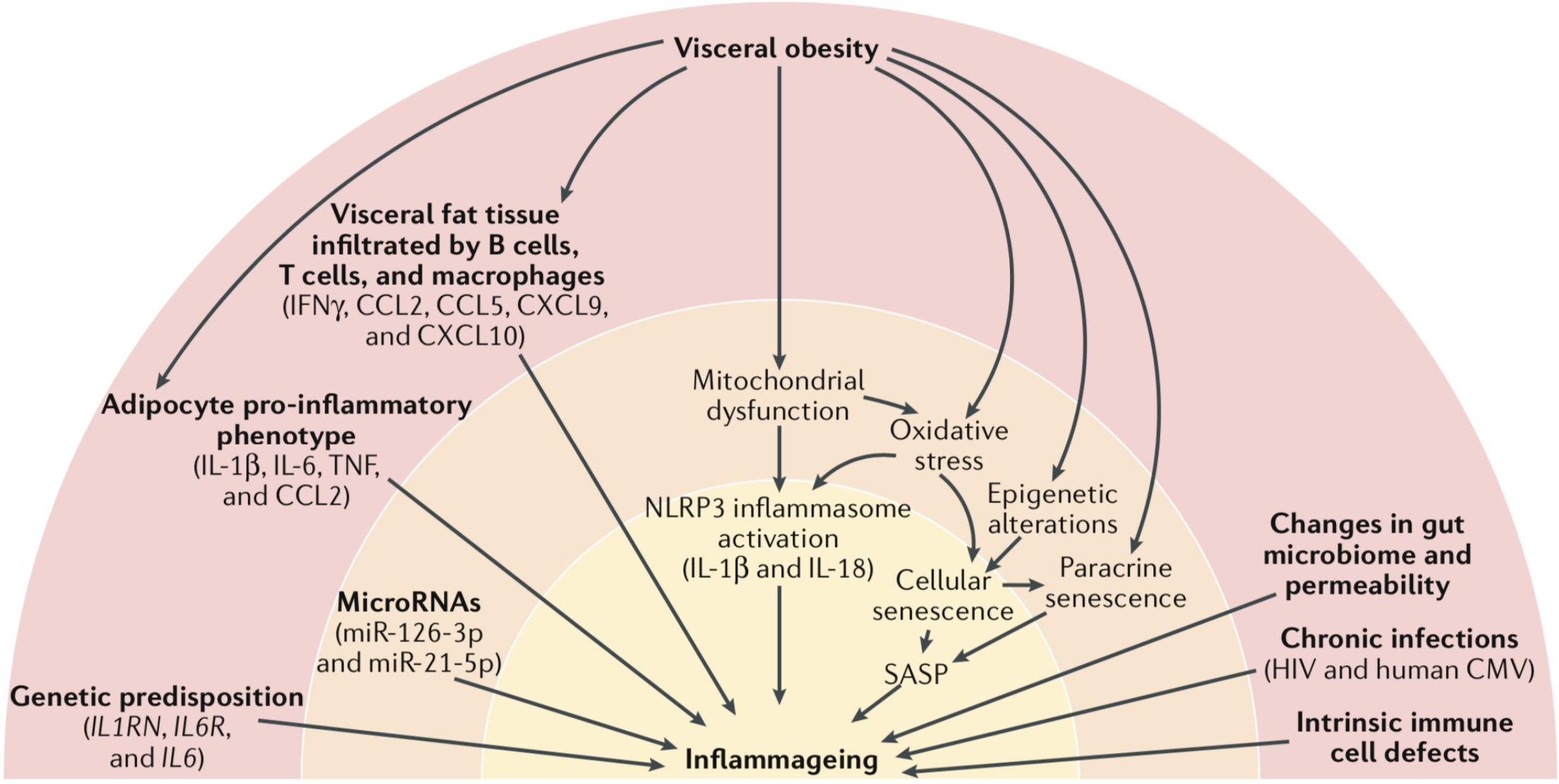


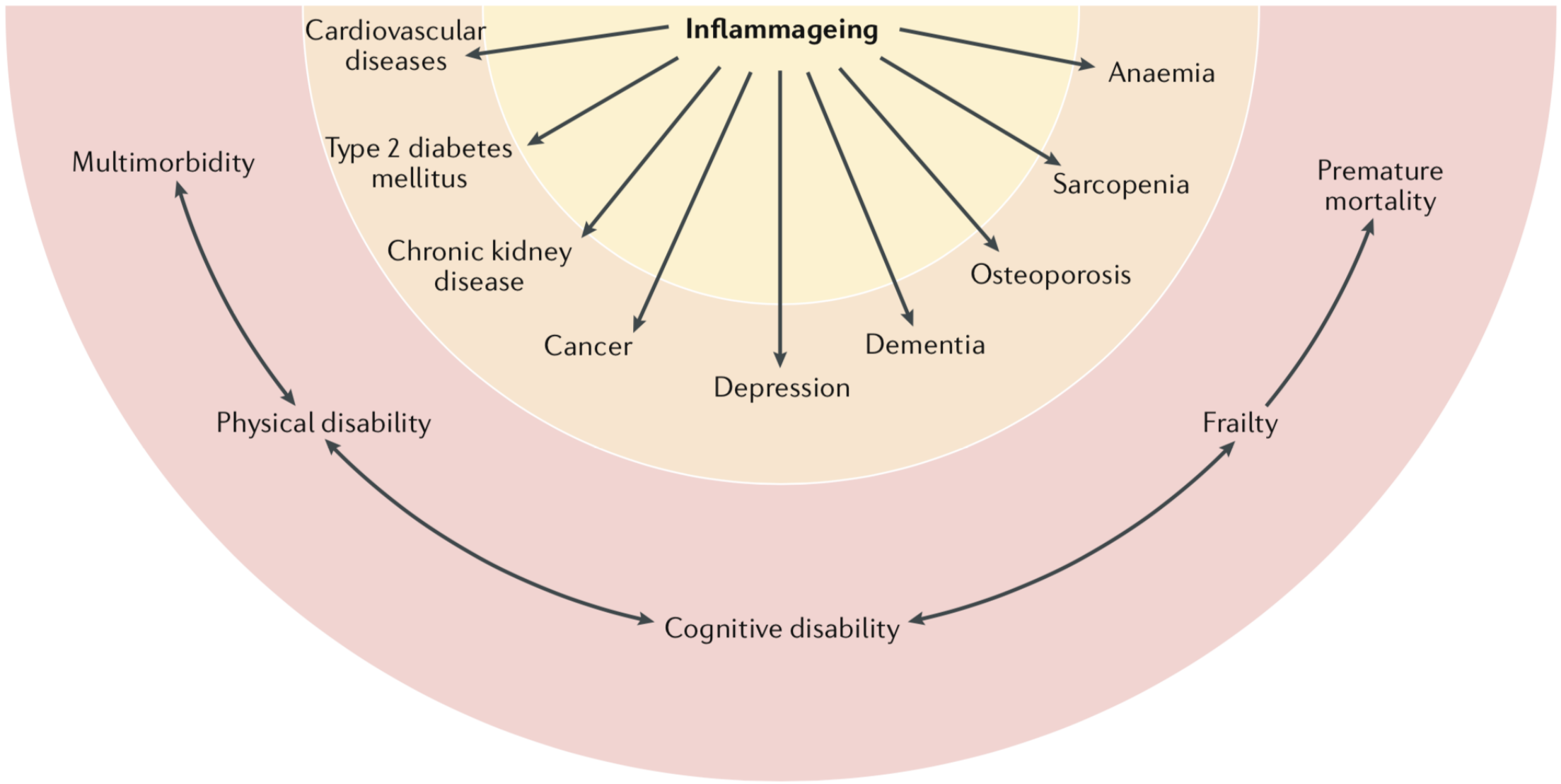
- Genomic instability
- Telomere attrition
- Epigenetic alterations
- Loss of proteostasis
- Disabled macroautophagy
- Deregulated nutrient-sensing
- Mitochondrial dysfunction
- Cellular senescence
- Stem cell exhaustion
- Altered intercellular communication
- **Chronic inflammation**
- Dysbiosis

Adapted from Lopez-Otin, Cell, 2023

Possible causes of inflammaging

Adapted from Ferrucci et al, Nat Rev, 2018





Possible consequences of inflammaging

Inflammaging biomarkers

Biomarker	Molecules involved	Effects
Pro-inflammatory and anti-inflammatory cytokines	TNF, IL-1β, IL-6, IL-8, TGF-β, IL-10, CXCL9	Circulating biomarkers of chronic inflammation (IL-6 central role in inflammaging)
Other plasma soluble factors	CRP Fibrinogen	
N-linked glycan profile	Serum IgG-G0 digalactosylated or agalactosylated N-linked glycan structures	Biological age (pathological vs non-pathological ageing)
DNA methylation	353 CpG sites in ELOVL2 that wwere used to construct the epigenetic clock to estimate the methylation age	Chronological age and biological age
Circulating miRNA	miR-155 mIR-21 mIR-146a	Systemic inflammation
Metabolomics and lipidomics	Glycerophosphoethanolamines Glycerophosphocholines Glycerolipids Bile acids Steroids Isoprenoids Fatty amides Sphinolipids Trp levels L-carnitine esters	Healthy aging (centenarians)
Circulating cf-mtDNA	Cf-mtDNA	Systemic inflammation

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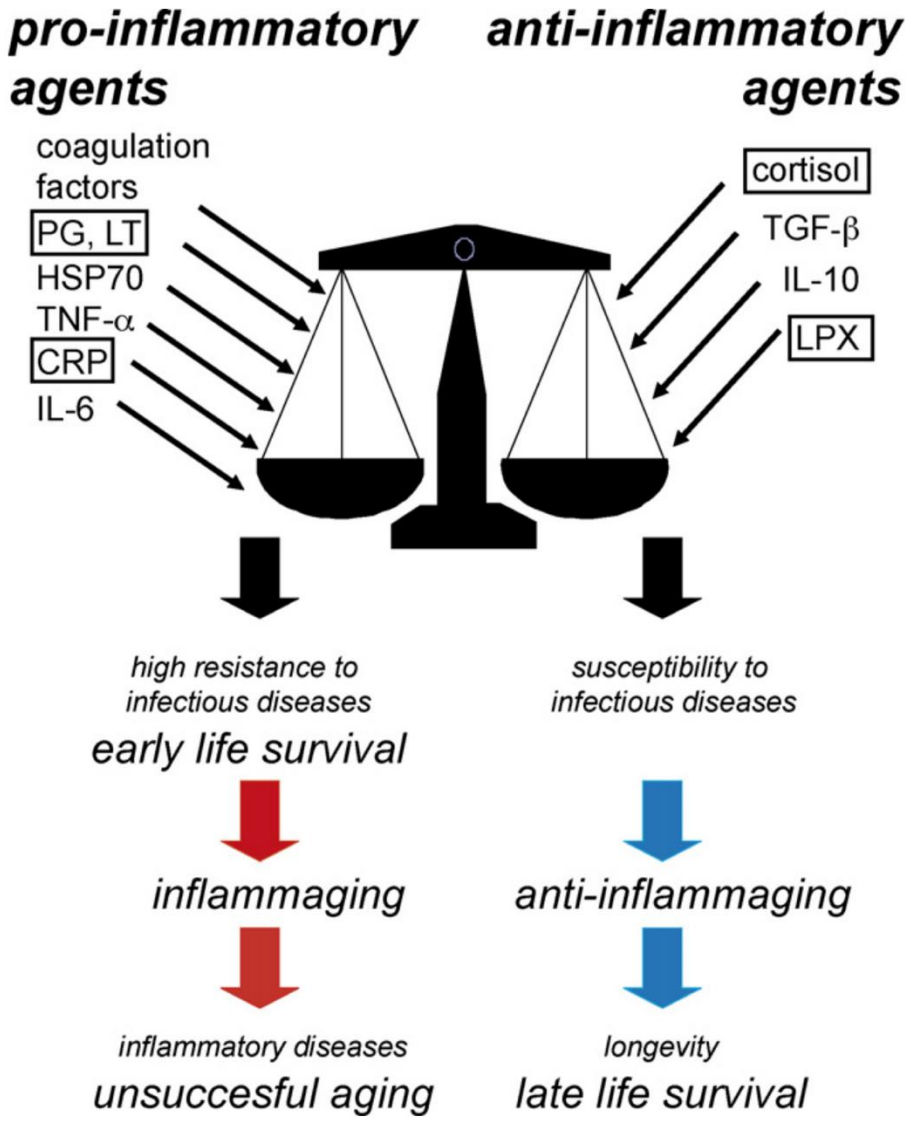
Inflammaging *vs* anti-inflammaging

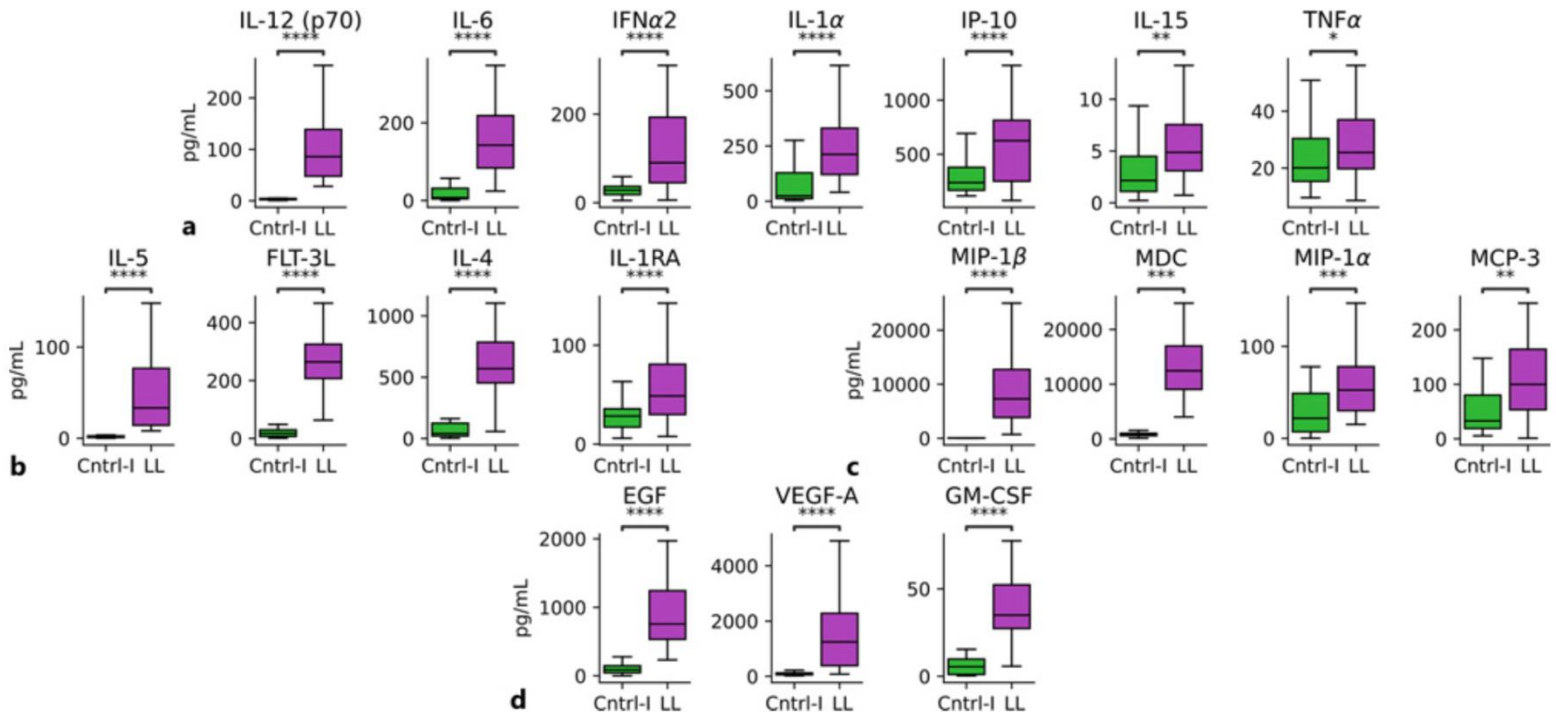


Adapted from Franceschi et al, Mech Age Develop, 2006

Inflammaging *vs* anti-inflammaging

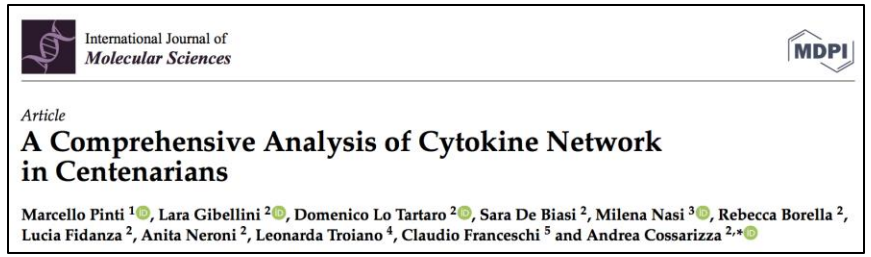
The most longeve humans seem to be equipped with gene variants that allow them **to optimize the balance between pro- and anti-inflammatory molecules**.

Thus, their immune system is able to **minimize** the effects of the lifelong exposure to environmental insults and stressors.



Chulenbayeva L. *et al.*, Gerontology 2024

PCA of plasma cytokine dataset identifies groups of donors, *i.e.* middle-aged donors vs. centenarians

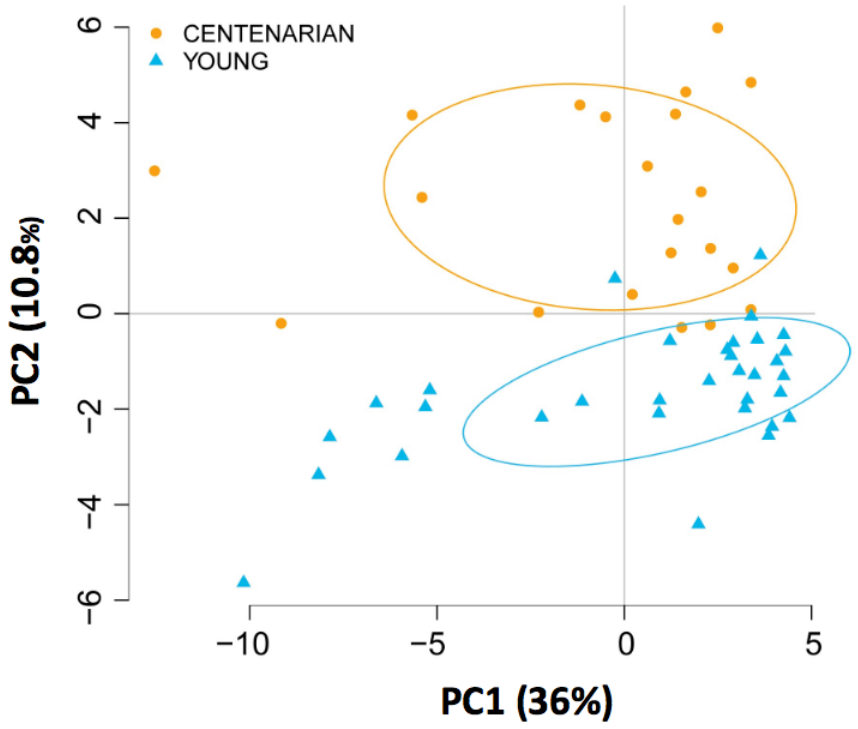

International Journal of *Molecular Sciences*

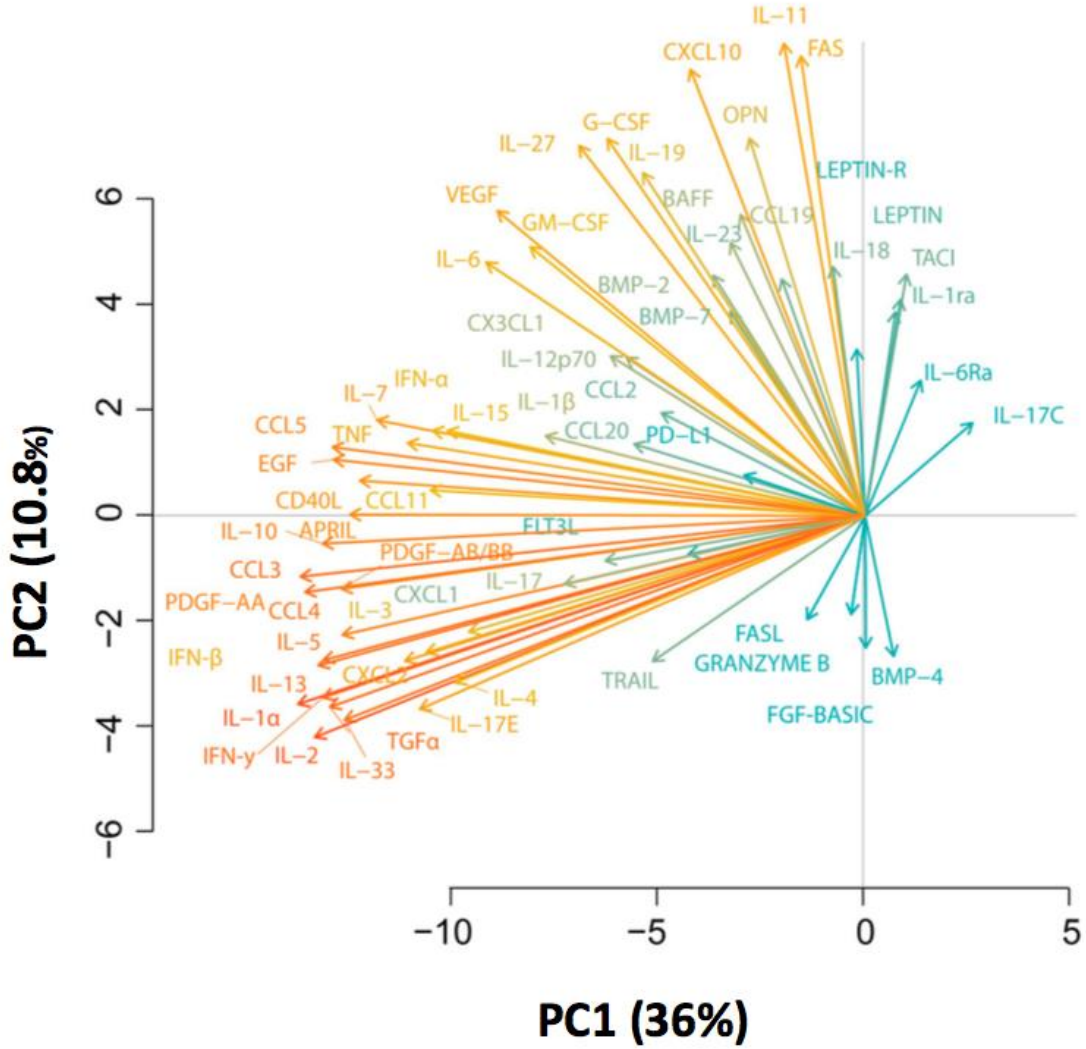
MDPI

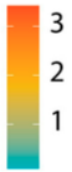
Article

A Comprehensive Analysis of Cytokine Network in Centenarians

Marcello Pinti [1], Lara Gibellini [2], Domenico Lo Tartaro [2], Sara De Biasi [2], Milena Nasi [3], Rebecca Borella [2], Lucia Fidanza [2], Anita Neroni [2], Leonarda Troiano [4], Claudio Franceschi [5] and Andrea Cossarizza [2,*]







Contribution of variables to PCA

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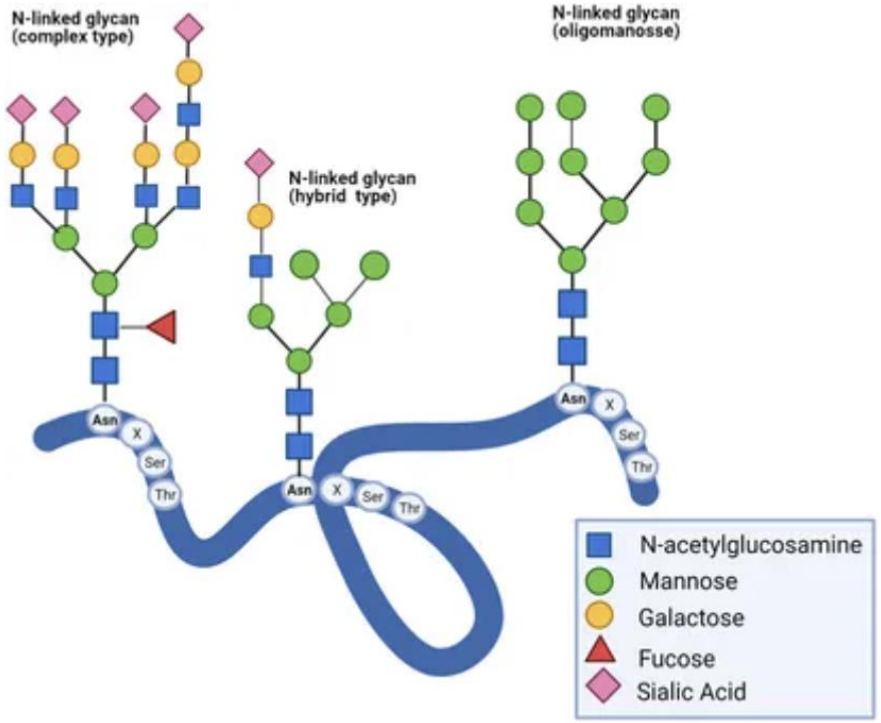
N-glycans



The log ratio of the relative abundance of two *N*-linked glycan species (namely, agalacto core-α-1,6-fucosylated diantennary glycan (NGA2F) and digalacto core-α-1,6-fucosylated diantennary glycan (NA2F)) increases progressively with age and is associated with features of healthy and unhealthy ageing.

Loaeza-Reyes L. *et al.*, Frontiers in Immunol, 2021

N-glycans and inflammaging

- Protein galactosylation is responsible for the anti-inflammatory function of immunoglobulin G (IgG)
- With increasing age, the galactosylated biantennary structures that decorate the Asn297 of the crystallizable fragment (Fc) portion of IgG become devoid of galactose at both branches (called **IgG-G0**) and become highly pro-inflammatory.
- The study proposed to use IgG-G0 as a biomarker of inflammatory conditions during ageing, in which chronic low-grade inflammatory pathways negatively affect the glycosylation machinery of antibody-producing cells.

Loaeza-Reyes L. *et al.*, Frontiers in Immunol, 2021

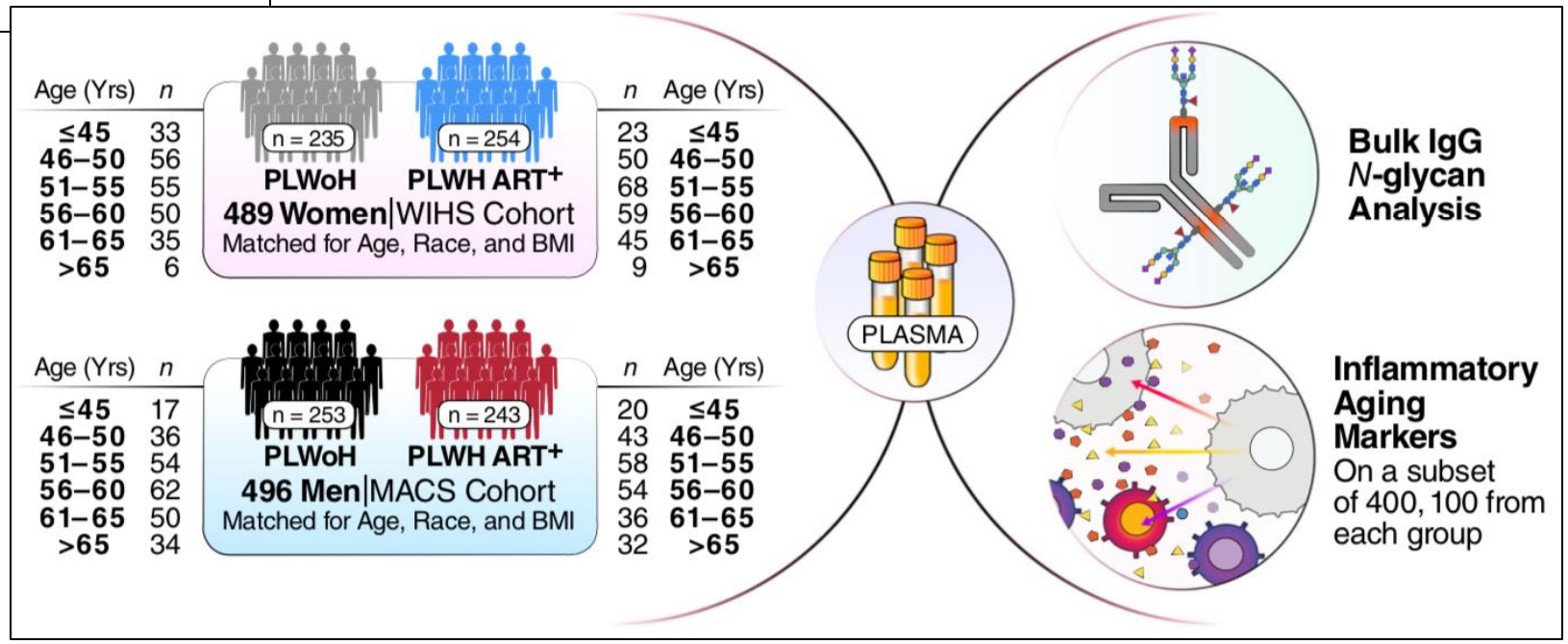
N-glycans markers of accelerated biological aging during chronic HIV infection

nature communications

Article

https://doi.org/10.1038/s41467-024-47279-4

Immunoglobulin G *N*-glycan markers of accelerated biological aging during chronic HIV infection



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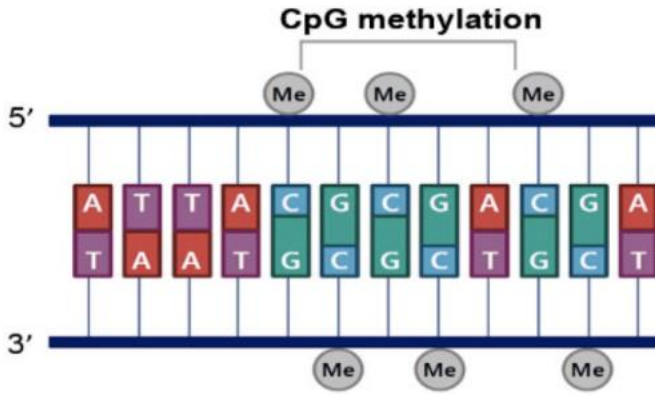
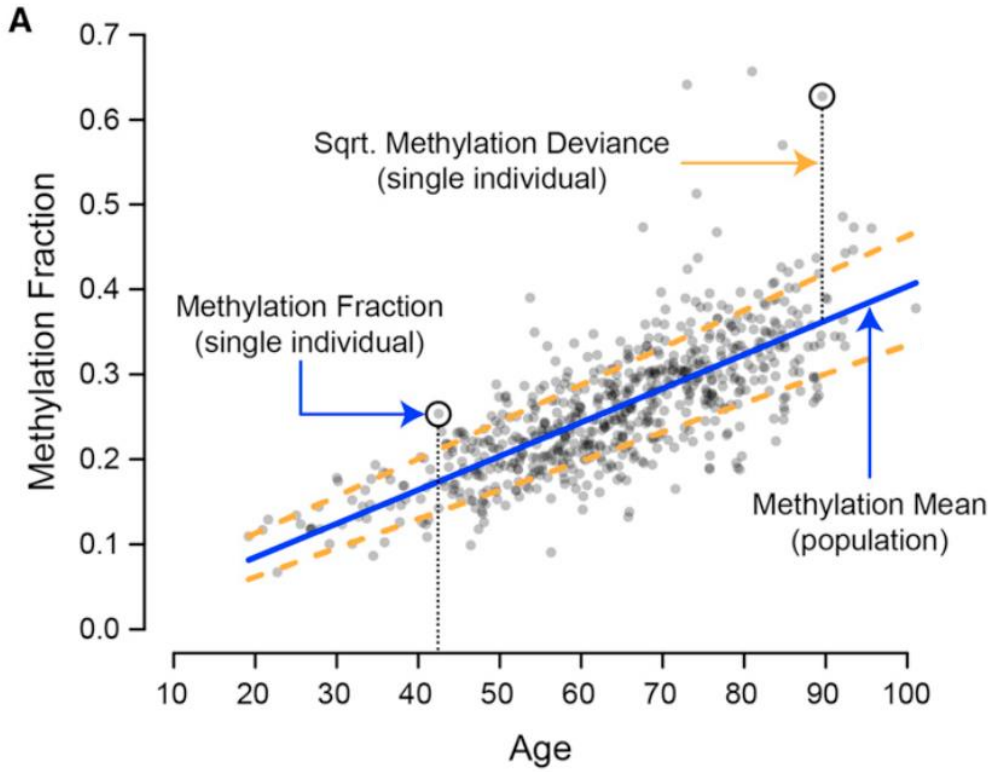
Methylation profiles and human aging



CpG methylation is a form of DNA modification where a methyl group is added to a cytosine base within a CpG dinucleotide



Fast aging

Slow aging

DNA mehylation is a biomarker of chronological aging and biological aging

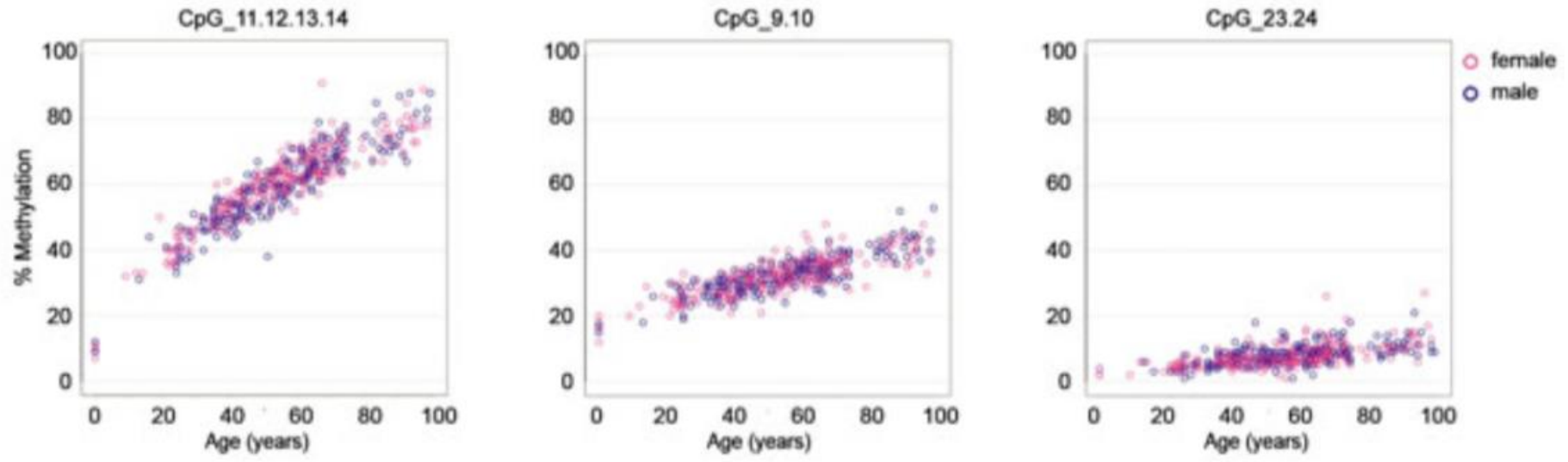
Hannum L. *et al.*, Mol Cell, 2013

Methylation profile of *ELOVL2* promoter

Aging Cell (2012) **11**, pp1132–1134 Doi: 10.1111/acel.12005

SHORT TAKE

Methylation of *ELOVL2* gene as a new epigenetic marker of age



ELOVL2 *FHL2* *PENK*

Garagnani *et al.*, Aging Cell, 2012

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Circulating cf-mtDNA	Cf-mtDNA	Systemic inflammation

Lipid and metabolic profiles and aging

- Centenarians had a peculiar lipid profile, with unique changes in 41 of 161 measured lipid species.
- The lipid profile emphasized that long-living individuals have marked features of anti-inflammatory molecules, such as increased levels of **phenylalanine**, which inhibits the nuclear factor-κB (NF-κB) pathway, and decreased levels of **glycerophosphocholine** (a circulating marker of cellular senescence). Monotliu et al, Aging, 2014
- Female familial longevity were identified. A profile that included high levels of phosphocholine and sphingomyelin and low levels of **phosphoethanolamine** and **long-chain triglyceride species** was found to be characteristic of healthy ageing. Gonzalez-Covarrubias et al, Aging Cell, 2013
- The plasma and urine from centenarians showed changes in the levels of specific glycerophospholipids and sphingolipids and a decrease in tryptophan concentration. Collino et al, Plos One, 2013.

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Mitochondria and inflammation

CLINICAL IMMUNOLOGY

Culprits with evolutionary ties

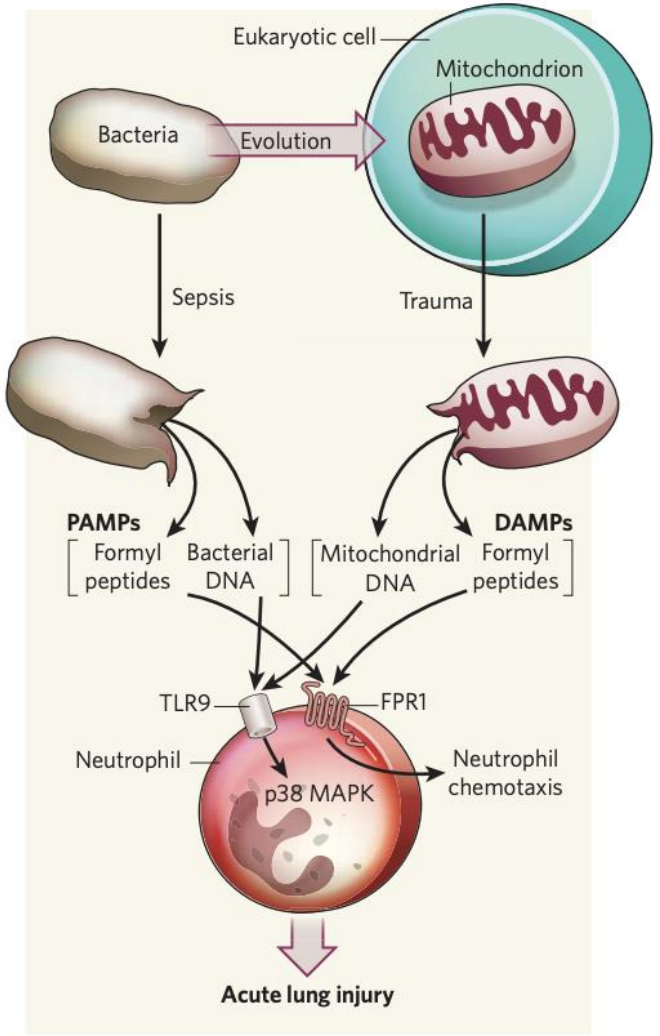
Carolyn S. Calfee and Michael A. Matthay

The cellular organelles we know as mitochondria are thought to have originated as symbiotic bacteria. Indeed, the two use common mechanisms to trigger innate immune responses to injury and infection, respectively.

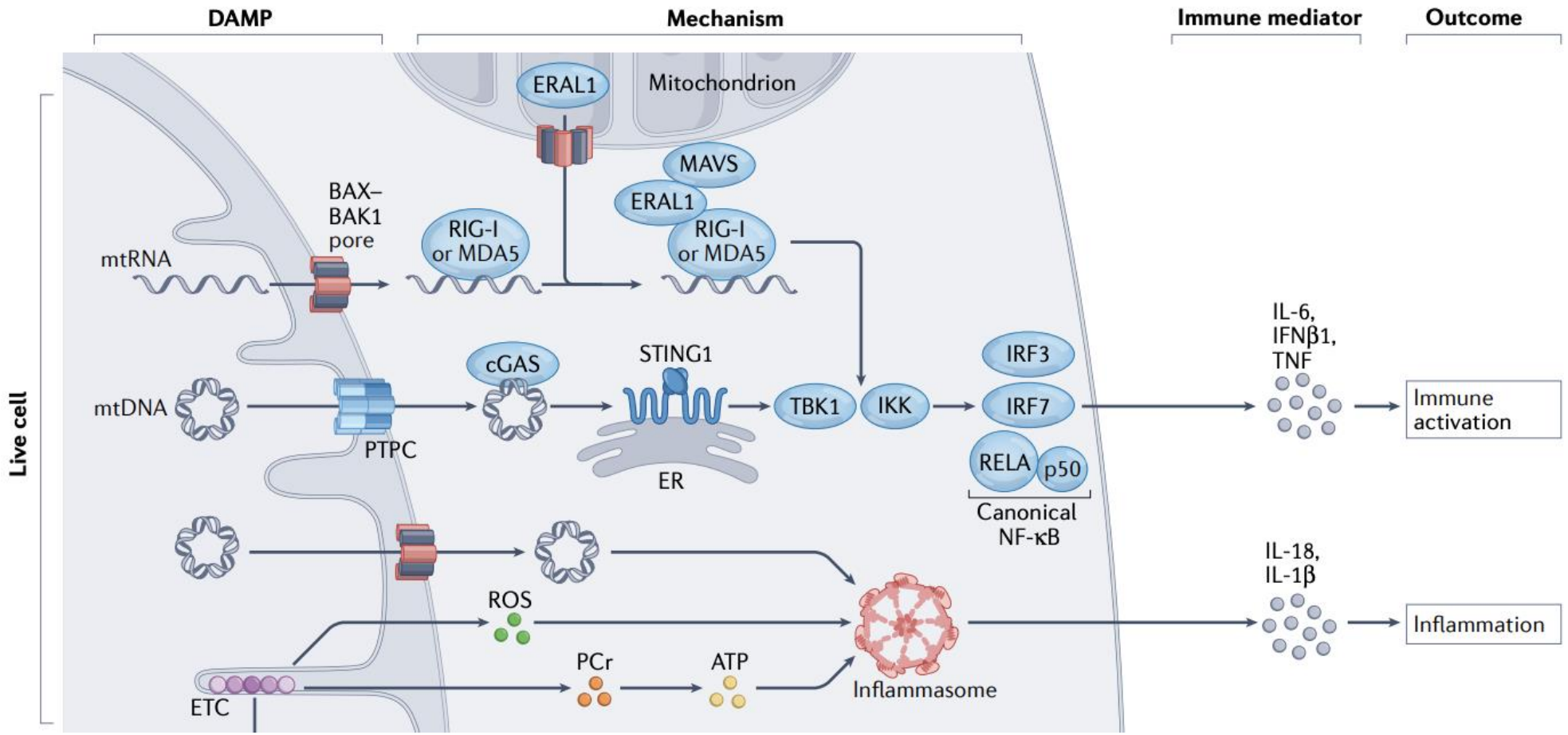
Mitochondria have originated as symbiotic bacteria

↓

They use common mechanisms to trigger INNATE IMMUNE RESPONSES to injury and infection



Mitochondria and inflammation



mtDNA: DANGER SIGNAL

Marchi L. *et al.*, NAt Rev Immunol, 2024

Plasma mtDNA increases with aging

Marcello Pinti et al. DOI: 10.1002/eji.201343921 Eur. J. Immunol. 2014. 44: 1552–1562

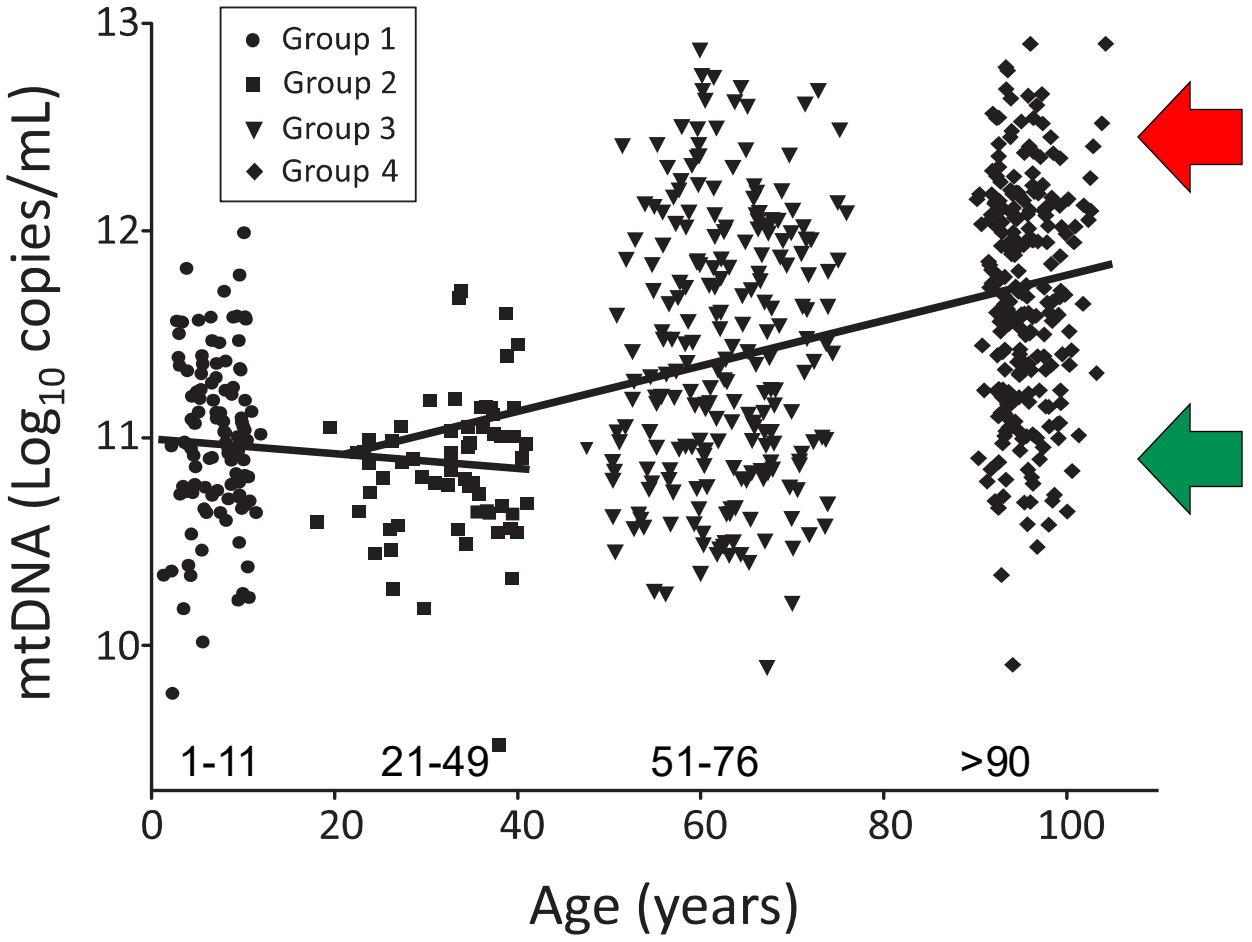
European Journal of Immunology

Circulating mitochondrial DNA increases with age and is a familiar trait: Implications for "inflamm-aging"

Marcello Pinti[*1], *Elisa Cevenini*[*2,3], *Milena Nasi*[4], *Sara De Biasi*[4], *Stefano Salvioli*[2,3], *Daniela Monti*[5], *Stefania Benatti*[1], *Lara Gibellini*[4], *Rodolfo Cotichini*[6,7], *Maria Antonietta Stazi*[6], *Tommaso Trenti*[8], *Claudio Franceschi*[2,3] *and Andrea Cossarizza*[4]

Linear Regression for log 10 mt DNA by age

Groups	Number of obs.	R-squared	Beta Co eff.	Age p	95% CI	
Group 1 and 2	171	0.0215	-0.0045	0.055	-0.0091	0.0001
Group 2, 3 and 4	516	0.1590	0.0115	<0.001	0.0092	0.0138



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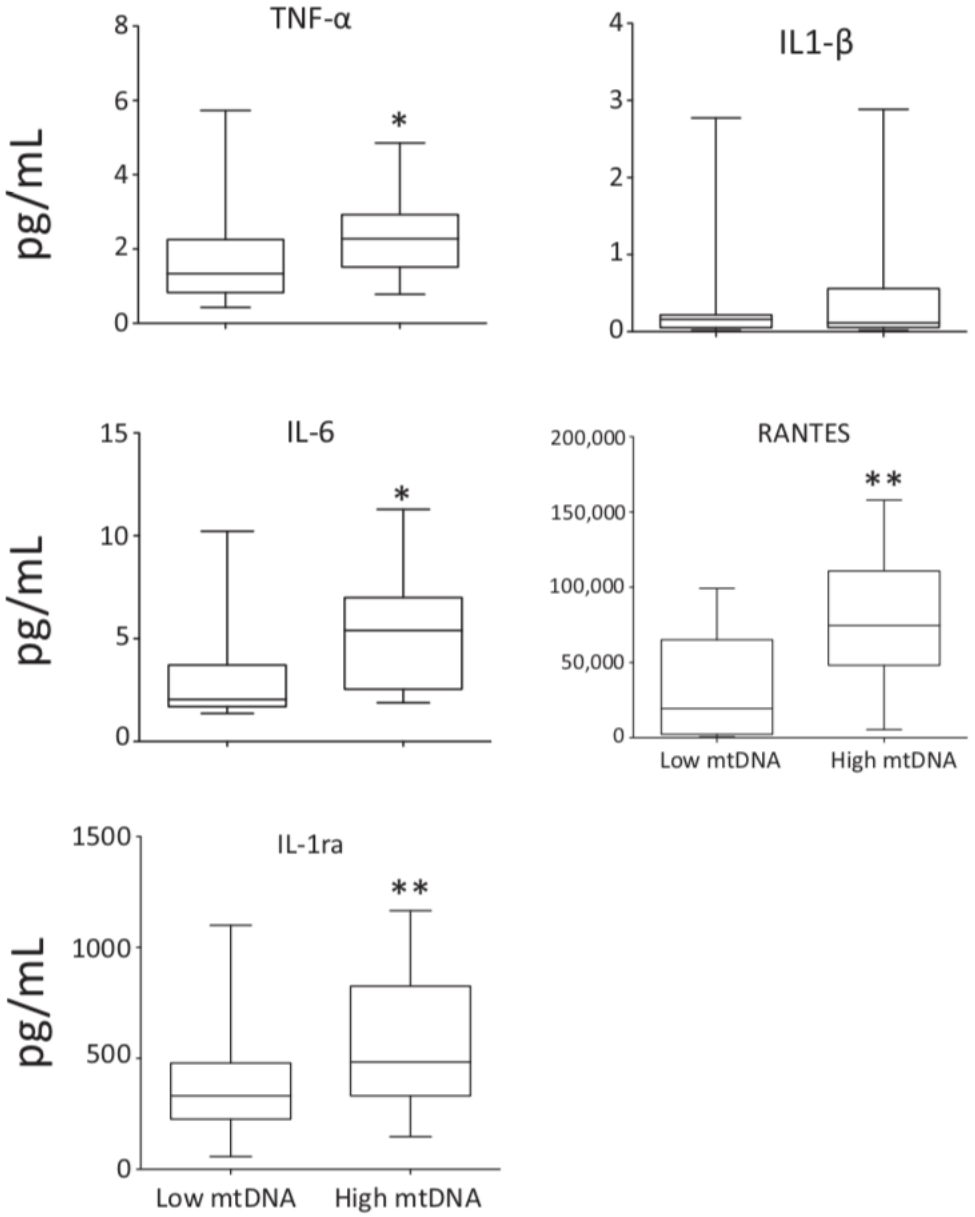


Lymphoma and inflammaging

- **Chronic immune activation**
  Persistent inflammation can cause DNA damage and promote mutations in lymphocytes.

- **Immunosenescence**
  Aging impairs immune surveillance, making it easier for malignant clones to escape detection.

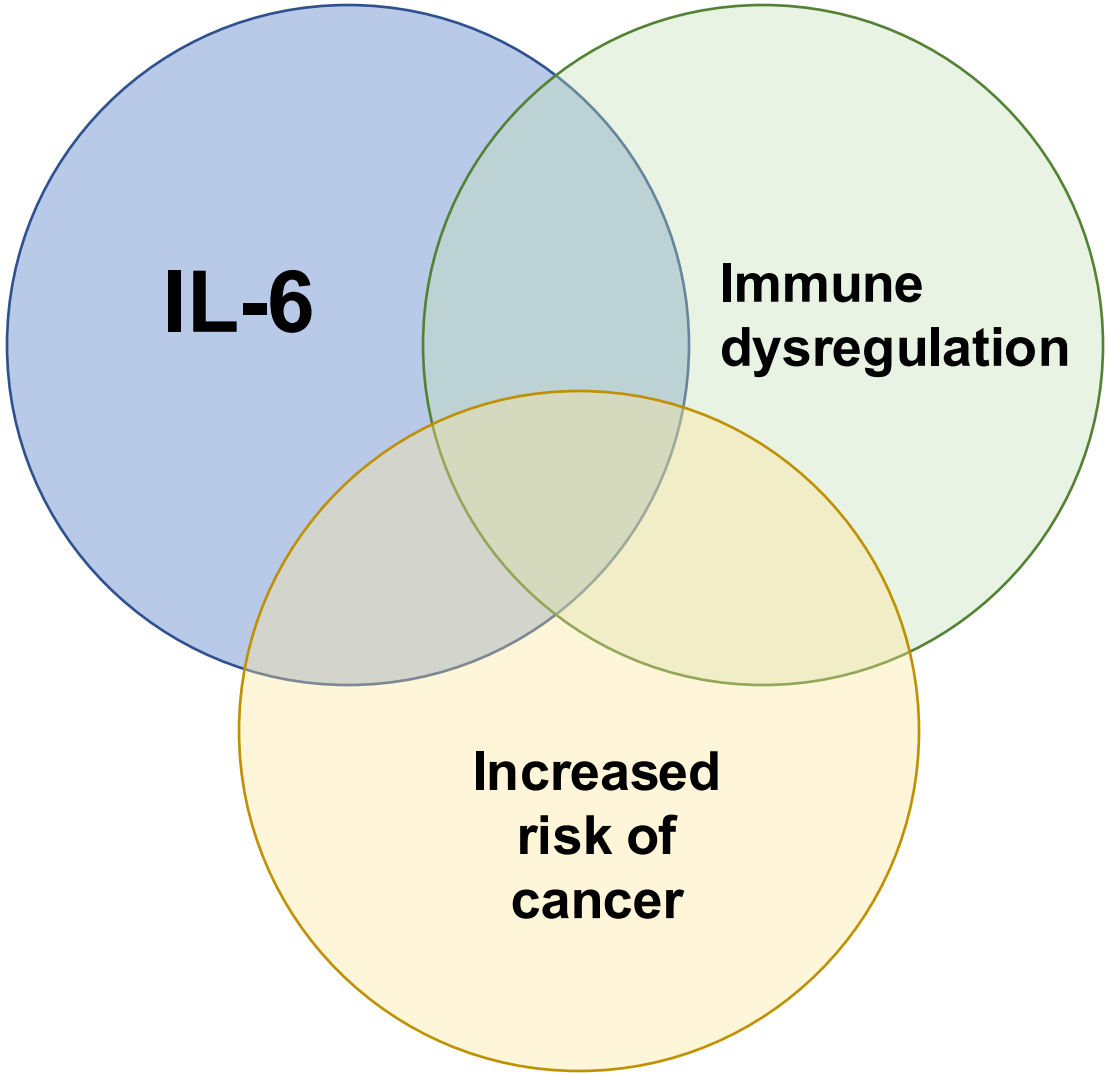
- **Microenvironmental changes**
  Inflammaging alters the tissue microenvironment, which may support lymphoma growth and survival.

- **Cytokine imbalance**
  Pro-inflammatory cytokines involved in inflammaging may contribute to the growth and survival of lymphoma cells.

Clinical Implications

Age-adjusted treatment strategies are critical in older lymphoma patients, who may also be affected by inflammaging-related frailty.

Castelman disease and inflammaging



Conclusions

- Low-grade, chronic state of inflammation
- Inflammaging has multiple and heterogeneous causes
- Inflammaging has multiple and heterogeneous consequences
- Inflammaging can be measured
- There are several links between inflammaging and lymphoma, and between inflammaging and Castelman disease

Acknowledgements

Immunology Lab
University of Modena and Reggio Emilia (Italy)

Andrea Cossarizza (Head)
Sara De Biasi
Domenico Lo Tartaro
Elena Santacroce
Alin Liviu Ciobanu
Miriam D'Angerio
Maristella Leccese