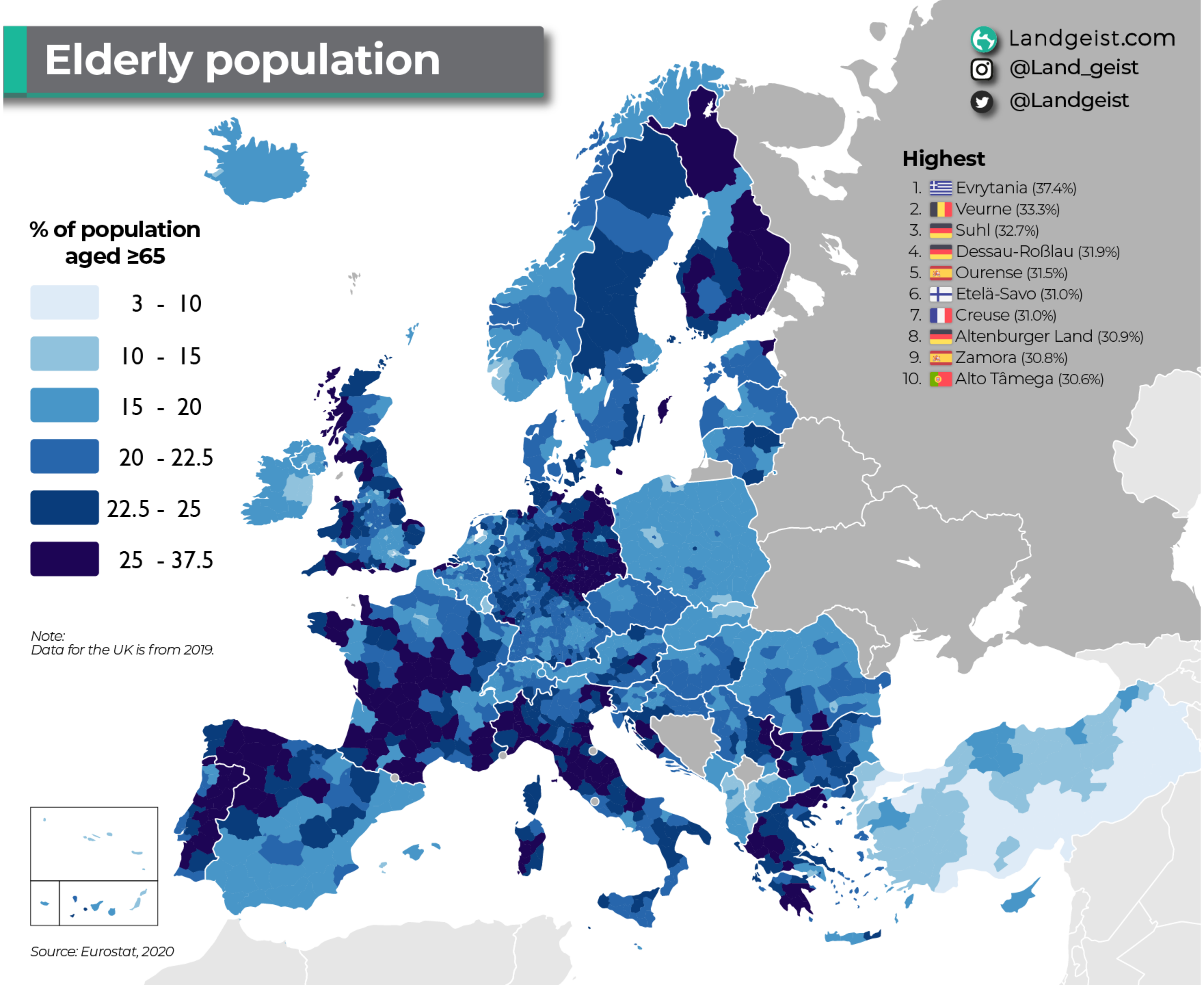
TARTU ÜLIKOOL
1632

T cell aging

Pärt Peterson

Institute of Biomedicine and Translational Medicine
University of Tartu, Estonia


Elderly population
Landgeist.com
@Land_geist
@Landgeist
% of population aged ≥65
3 - 10
10 - 15
15 - 20
20 - 22.5
22.5 - 25
25 - 37.5
Note:
Data for the UK is from 2019.
Source: Eurostat, 2020
Highest
1. Evrytania (37.4%)
2. Veurne (33.3%)
3. Suhl (32.7%)
4. Dessau-Roßlau (31.9%)
5. Ourense (31.5%)
6. Etelä-Savo (31.0%)
7. Creuse (31.0%)
8. Altenburger Land (30.9%)
9. Zamora (30.8%)
10. Alto Tâmega (30.6%)

Most immunological variation occurs during life

- **Human immunological variation is associated with age, CMV infection, stress, smoking, and metabolic health**
- **There are only few longitudinal studies of changes in the human immune system**

Variation in the Human Immune System Is Largely Driven by Non-Heritable Influences

Petter Brodin,[1,2,3,11] Vladimir Jojic,[4,11] Tianxiang Gao,[4] Sanchita Bhattacharya,[3] Cesar J. Lopez Angel,[2,3] David Furman,[2,3] Shai Shen-Orr,[5] Cornelia L. Dekker,[6] Gary E. Swan,[7] Atul J. Butte,[6,8] Holden T. Maecker,[3,9] and Mark M. Davis[2,3,10,*]
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http://dx.doi.org/10.1016/j.cell.2014.12.020

Genetic Variants Regulating Immune Cell Levels in Health and Disease

Valeria Orrù,[1,12] Maristella Steri,[1,12] Gabriella Sole,[1] Carlo Sidore,[1,2,3] Francesca Virdis,[1] Mariano Dei,[1] Sandra Lai,[1] Magdalena Zoledziewska,[1] Fabio Busonero,[1] Antonella Mulas,[1,3] Matteo Floris,[4] Wieslawa I. Mentzen,[1] Silvana A.M. Urru,[4] Stefania Olla,[1] Michele Marongiu,[1] Maria G. Piras,[1] Monia Lobina,[1,3] Andrea Maschio,[1,2] Maristella Pitzalis,[1] Maria F. Urru,[4] Marco Marcelli,[4] Roberto Cusano,[1,4] Francesca Deidda,[1,4] Valentina Serra,[1,3] Manuela Oppo,[4] Rosella Pilu,[1,4] Frederic Reinier,[4] Riccardo Berutti,[3,4] Luca Pireddu,[4,5] Ilenia Zara,[4] Eleonora Porcu,[1,3] Alan Kwong,[2] Christine Brennan,[11] Brendan Tarrier,[11] Robert Lyons,[11] Hyun M. Kang,[2] Sergio Uzzau,[3,6] Rossano Atzeni,[4] Maria Valentini,[4] Davide Firinu,[7] Lidia Leoni,[4] Gianluca Rotta,[8] Silvia Naitza,[1] Andrea Angius,[1,4] Mauro Congia,[9] Michael B. Whalen,[1] Chris M. Jones,[4] David Schlessinger,[10] Gonçalo R. Abecasis,[2] Edoardo Fiorillo,[1,12,*] Serena Sanna,[1,12,*] and Francesco Cucca[1,3,12,*]

Article

Human Immune System Variation during 1 Year

Tadepally Lakshmikanth,[1,6] Sayyed Auwn Muhammad,[1,6] Axel Olin,[1,6] Yang Chen,[1] Jaromir Mikes,[1] Linn Fagerberg,[2] Anders Gummesson,[3,4] Göran Bergström,[3,4] Mathias Uhlen,[2] and Petter Brodin[1,5,7,*]
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Aging Cell WILEY

RESEARCH ARTICLE

Identification of aging-associated immunotypes and immune stability as indicators of post-vaccination immune activation

Alper Cevirgel[1,2] | Sudarshan A. Shetty[1,2] | Martijn Vos[1] | Nening M. Nanlohy[1] | Lisa Beckers[1] | Elske Bijvank[1] | Nynke Rots[1] | Josine van Beek[1] | Anne-Marie Buisman[1] | Debbie van Baarle[1,2]

Article

Smoking changes adaptive immunity with persistent effects

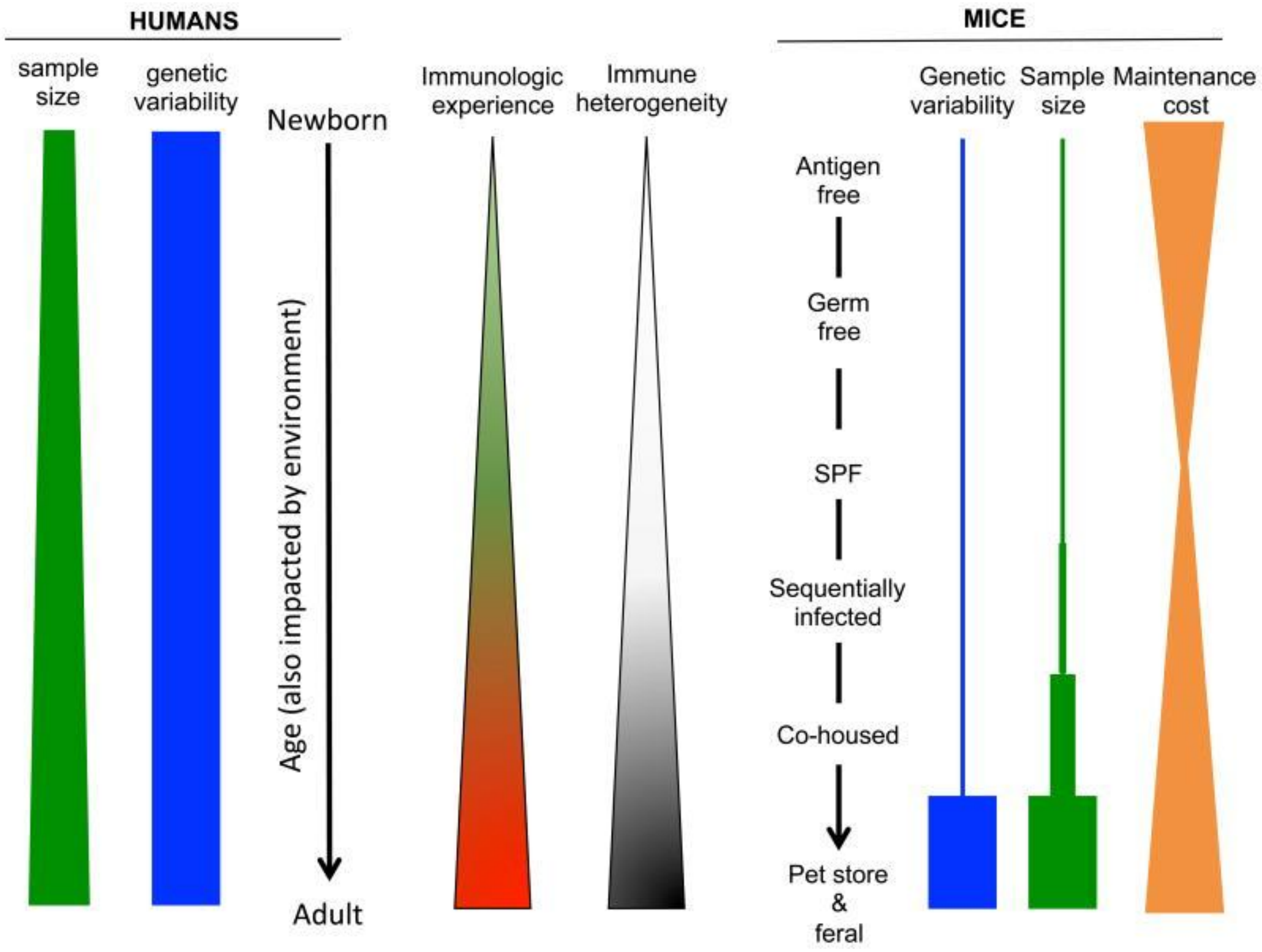
https://doi.org/10.1038/s41586-023-06968-8
Received: 1 November 2022
Accepted: 13 December 2023

Violaine Saint-André[1,2]✉, Bruno Charbit[3], Anne Biton[2], Vincent Rouilly[4], Céline Possémé[1], Anthony Bertrand[1,5], Maxime Rotival[6], Jacob Bergstedt[6,7,8], Etienne Patin[6], Matthew L. Albert[9], Lluis Quintana-Murci[6,10], Darragh Duffy[1,3]✉ & The Milieu Intérieur Consortium*

We know that age increases risk for immune-associated pathologies – but how?

- Increased susceptibility to infections
- Decreased response to vaccination
- Increased risk for chronic inflammatory diseases; cardiovascular, type 2 diabetes, chronic kidney disease
- Increased risk for autoimmune diseases
- Increased risk for cancers

Of mice and humans



Brief Reviews
The Journal of Immunology

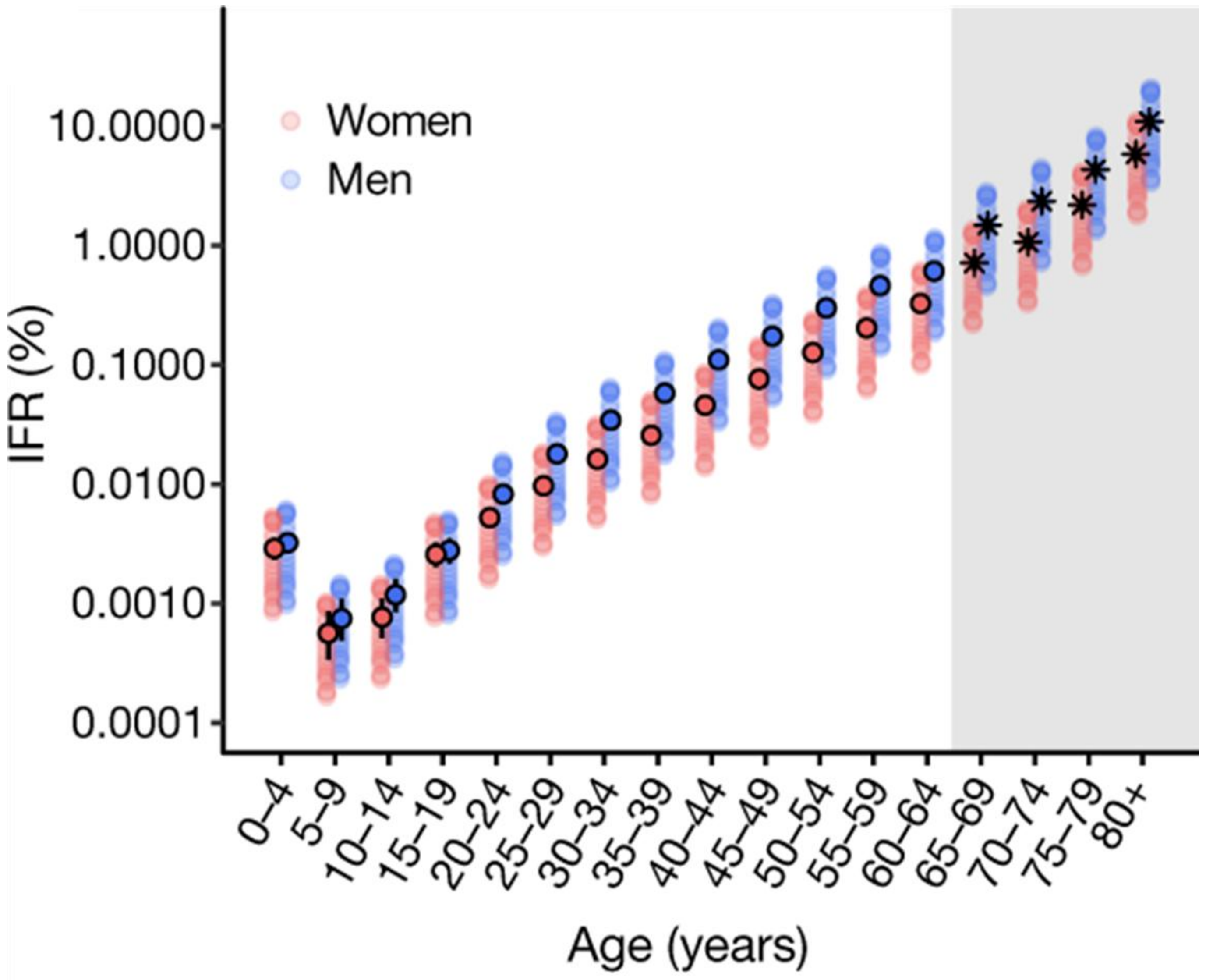
Of Mice, Dirty Mice, and Men: Using Mice To Understand Human Immunology

David Masopust,* Christine P. Sivula,† and Stephen C. Jameson‡

Mouse models have enabled breakthroughs in our understanding of the immune system, but it has become increasingly popular to emphasize their shortcomings when translating observations to humans. This review provides a brief summary of mouse natural history, husbandry, and the pros and cons of pursuing basic research in mice versus humans. Opportunities are discussed for extending the predictive translational value of mouse research, with an emphasis on exploitation of a "dirty" mouse model that better mimics the diverse infectious history that is typical of most humans. *The Journal of Immunology*, 2017, 199: 383–388.

groups called demes that are composed of a dominant breeding male, a hierarchy of females, subordinate males, and juveniles. This results in a high degree of inbreeding that, combined with their high mutation rates, contributes to their ability to adapt quickly to environmental changes (3, 4). Mice are omnivorous, nocturnal, adapt well to temperature extremes, and with their ability to jump and chew through small openings, they are well poised to take advantage of human food sources in fields, homes, and granaries (5). Although such behaviors prove beneficial for the survival and propagation of the mouse, consumption and contamination of food stores have prompted the view of mice as a pest species. However, hobbyists took an interest in breeding and

Infection fatality rate (IFR)



SARS-CoV-2 fatality rate

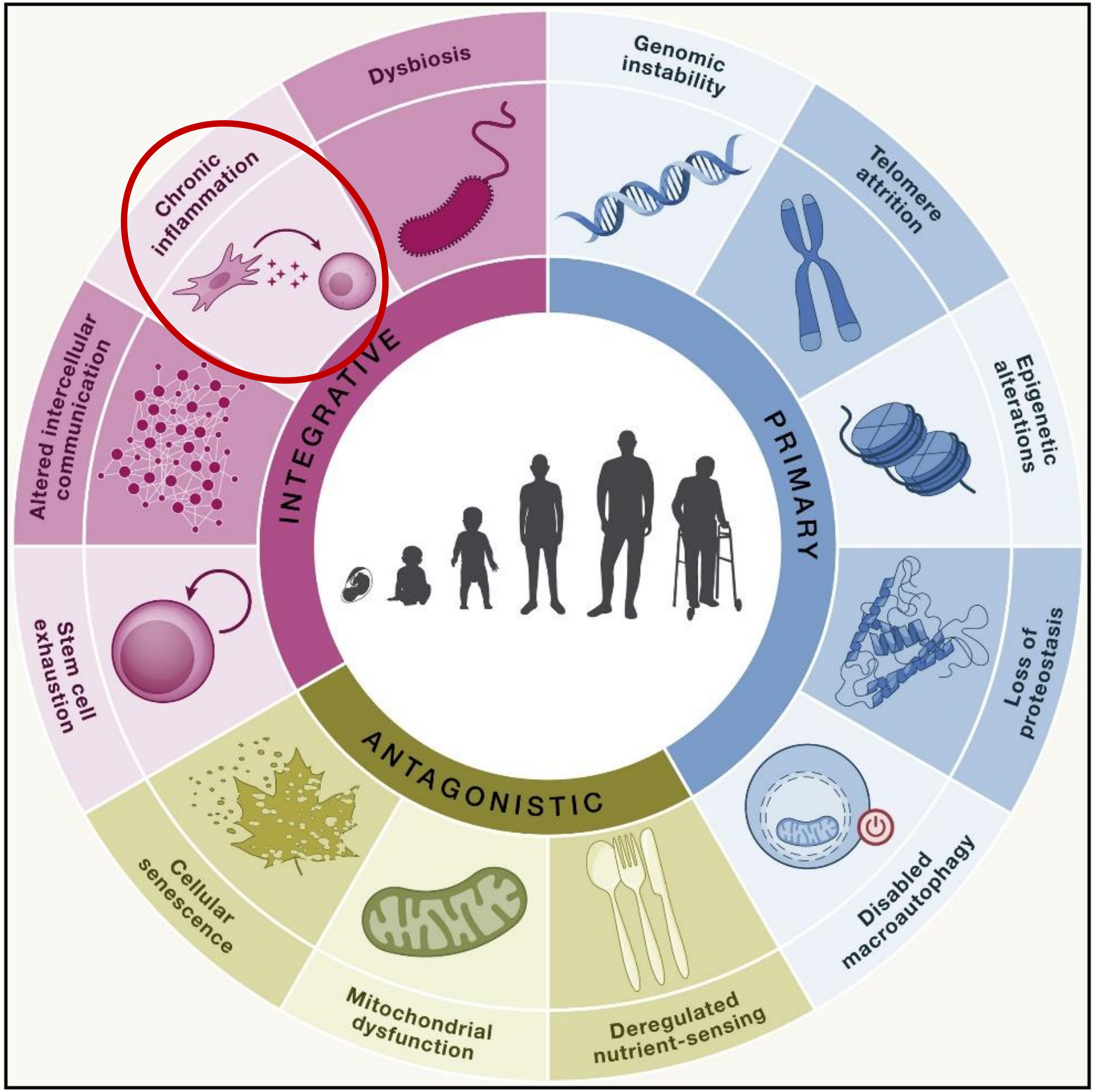
Old individuals and old societies at risk

11% men and 6% women at age 80+

O'Driscoll et al 2021 Age-specific mortality and immunity patterns of SARS-CoV-2. *Nature*

Vaccination efficiency is decreased in older individuals

Edward Jenner (1796)

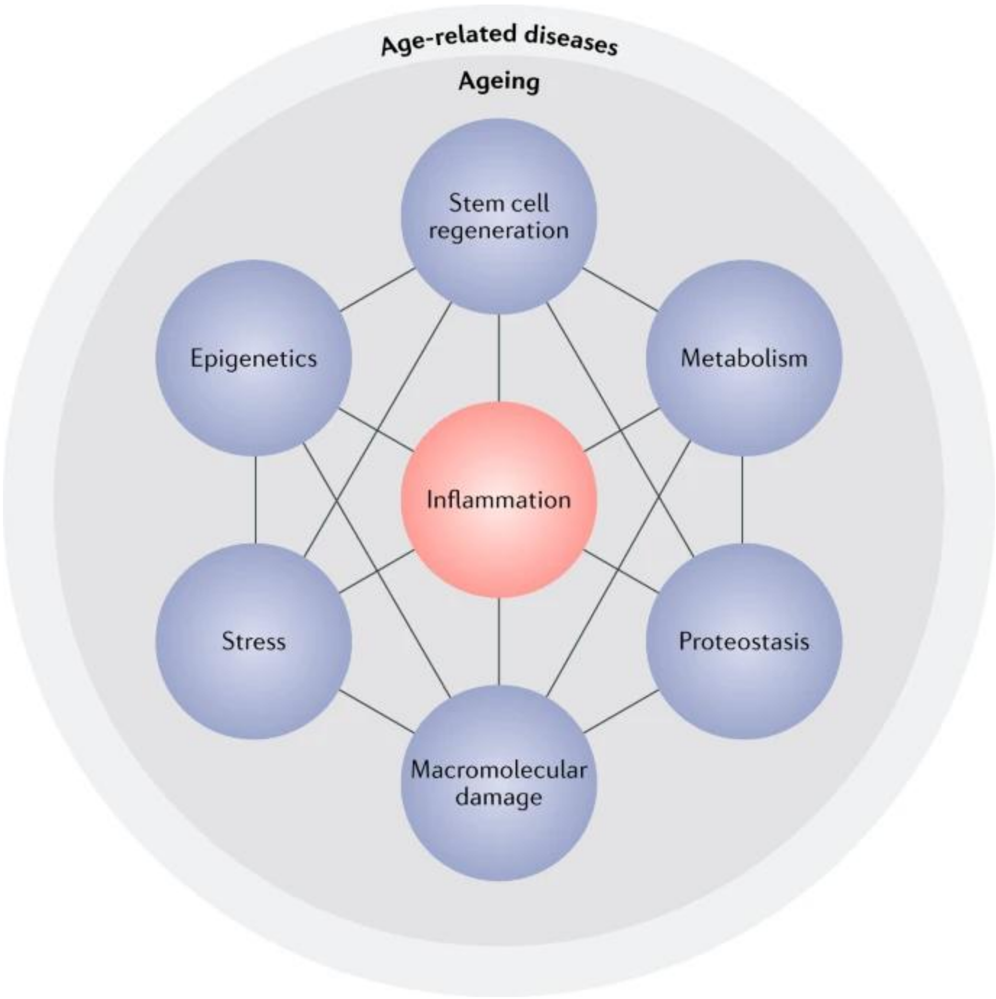


Age associated changes in cells

- Chronic inflammation
- Imbalance of the intestinal microflora
- Genomic instability
- Telomere shortening
- Epigenetic changes
- Proteome instability
- Deficient macroautophagy
- Non-absorption of nutrients
- Errors in mitochondrial function
- Cellular senescence
- Stem cell insufficiency
- Changes in intercellular communication

López-Otín et al. 2023 Cell.

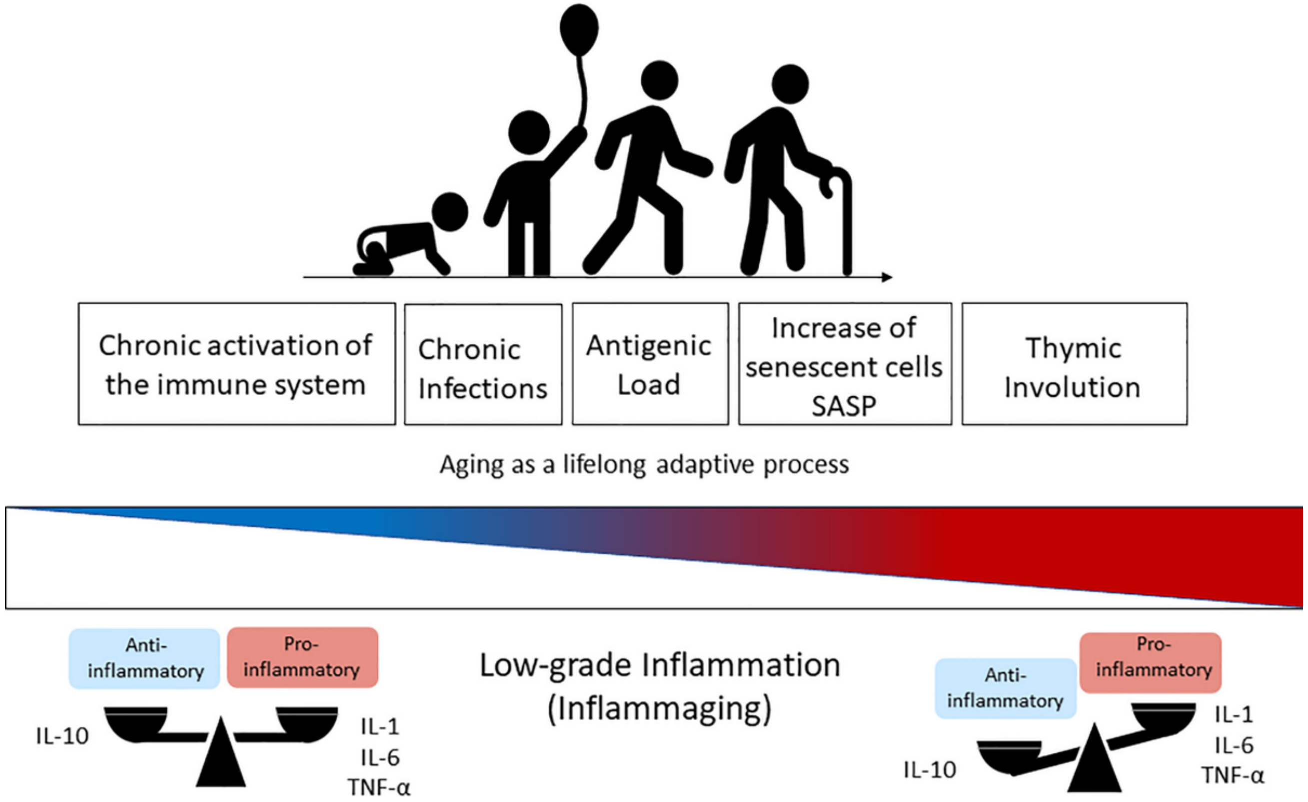
Chronic immune inflammation is associated with chronic diseases



Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty

Luigi Ferrucci[1] and Elisa Fabbri[2]*

Abstract | Most older individuals develop inflammageing, a condition characterized by elevated levels of blood inflammatory markers that carries high susceptibility to chronic morbidity, disability, frailty, and premature death. Potential mechanisms of inflammageing include genetic susceptibility, central obesity, increased gut permeability, changes to microbiota composition, cellular senescence, NLRP3 inflammasome activation, oxidative stress caused by dysfunctional mitochondria, immune cell dysregulation, and chronic infections. Inflammageing is a risk factor for cardiovascular diseases (CVDs), and clinical trials suggest that this association is causal.



Letter

https://doi.org/10.1038/s43587-025-00888-0

Nonuniversality of inflammaging across human populations

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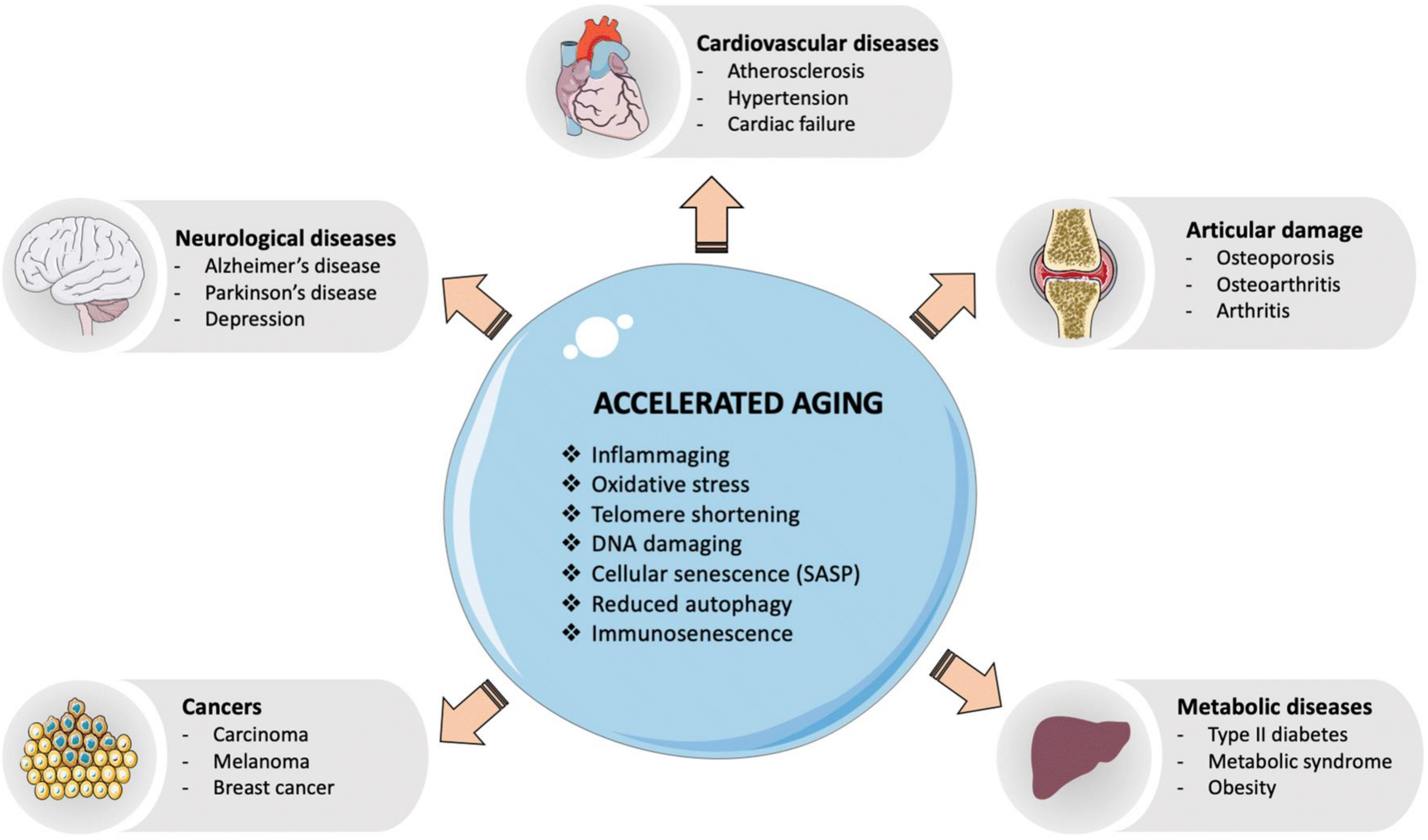
Accepted: 30 April 2025

Published online: 30 June 2025

Check for updates

Maximilien Franck[1], Kamaryn T. Tanner[2], Robert L. Tennyson[3,4], Camille Daunizeau[5], Luigi Ferrucci[6], Stefania Bandinelli[7], Benjamin C. Trumble[8], Hillard S. Kaplan[9], Jacob E. Aronoff[8], Jonathan Stieglitz[10], Thomas S. Kraft[11], Amanda J. Lea[3], Vivek V. Venkataraman[12], Ian J. Wallace[13], Yvonne A. L. Lim[14], Kee Seong Ng[15], Joe Poh Sheng Yeong[16,17,18,19], Roger Ho[20], Xinru Lim[16], Ameneh Mehrjerd[21], Eleftheria G. Charalambous[21], Allison E. Aiello[2,22], Graham Pawelec[23,24], Claudio Franceschi[25], Johannes Hertel[21,26], Tamàs Fülöp[1], Maël Lemoine[27], Michael Gurven[28] & Alan A. Cohen[1,2,29]

Chronic inflammation associated with multiple pathologies



Barbé-Tuana et al. 2020 Semin Immunopathol

Article

Clonally expanded CD8 T cells patrol the cerebrospinal fluid in Alzheimer's disease

https://doi.org/10.1038/s41586-019-1895-7
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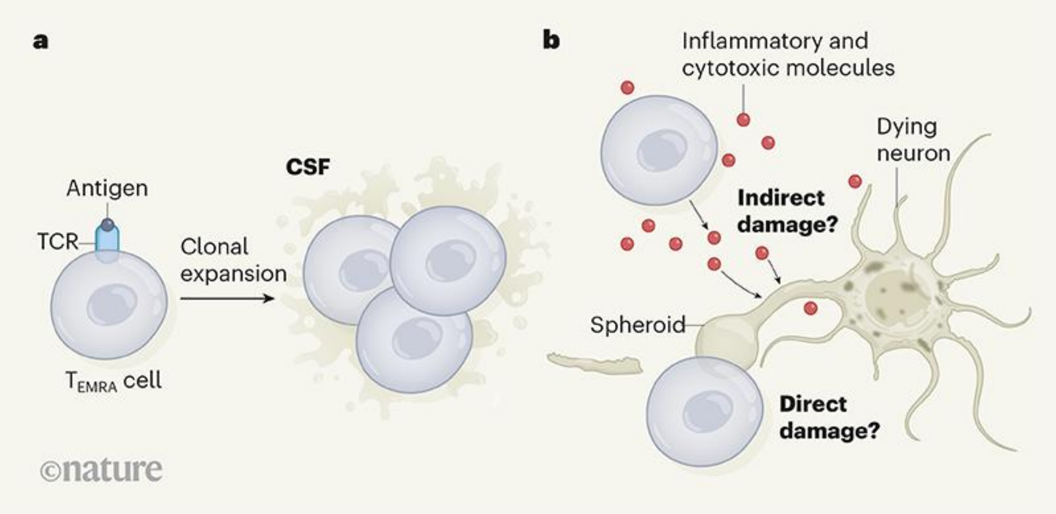
Accepted: 2 December 2019
Published online: 8 January 2020

David Gate[1,2*], Naresha Saligrama[3], Olivia Leventhal[1], Andrew C. Yang[4,5], Michael S. Unger[6,7], Jinte Middeldorp[1,2,8], Kelly Chen[1], Benoit Lehallier[1,2], Divya Channappa[1], Mark B. De Los Santos[1], Alisha McBride[1,2], John Pluvinage[1,9,10], Fanny Elahi[11], Grace Kyin-Ye Tam[1,12], Yongha Kim[1,12], Michael Greicius[1,12], Anthony D. Wagner[13,14], Ludwig Aigner[6,7], Douglas R. Galasko[15], Mark M. Davis[3,16,17] & Tony Wyss-Coray[1,2,5,14,18*]

peripheral blood mononuclear cells and discovered an immune signature of Alzheimer's disease that consists of increased numbers of CD8⁺ T effector memory CD45RA⁺ (T_{EMRA}) cells. In a second cohort, we found that CD8⁺ T_{EMRA} cells were negatively associated with cognition. Furthermore, single-cell RNA sequencing revealed that T cell receptor (TCR) signalling was enhanced in these cells. Notably, by using several strategies of single-cell TCR sequencing in a third cohort, we discovered clonally expanded CD8⁺ T_{EMRA} cells in the cerebrospinal fluid of patients with Alzheimer's disease. Finally, we used machine learning, cloning and peptide screens to demonstrate the specificity of clonally expanded TCRs in the cerebrospinal fluid of patients with Alzheimer's disease to two separate Epstein–Barr virus antigens. These



Received: 16 February 2023 | Revised: 17 April 2023 | Accepted: 18 April 2023
DOI: 10.1002/alz.13136

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

RESEARCH ARTICLE

Early β-amyloid accumulation in the brain is associated with peripheral T cell alterations

Christoph Gericke[1] | Tunahan Kirabali[1] | Roman Flury[2] | Anna Mallone[1,3] | Chiara Rickenbach[1] | Luka Kulic[1,4] | Vinko Tosevski[5] | Christoph Hock[1,6,7] | Roger M. Nitsch[1,7] | Valerie Treyer[1,6,8] | Maria Teresa Ferretti[1,9] | Anton Gietl[1,6,10]

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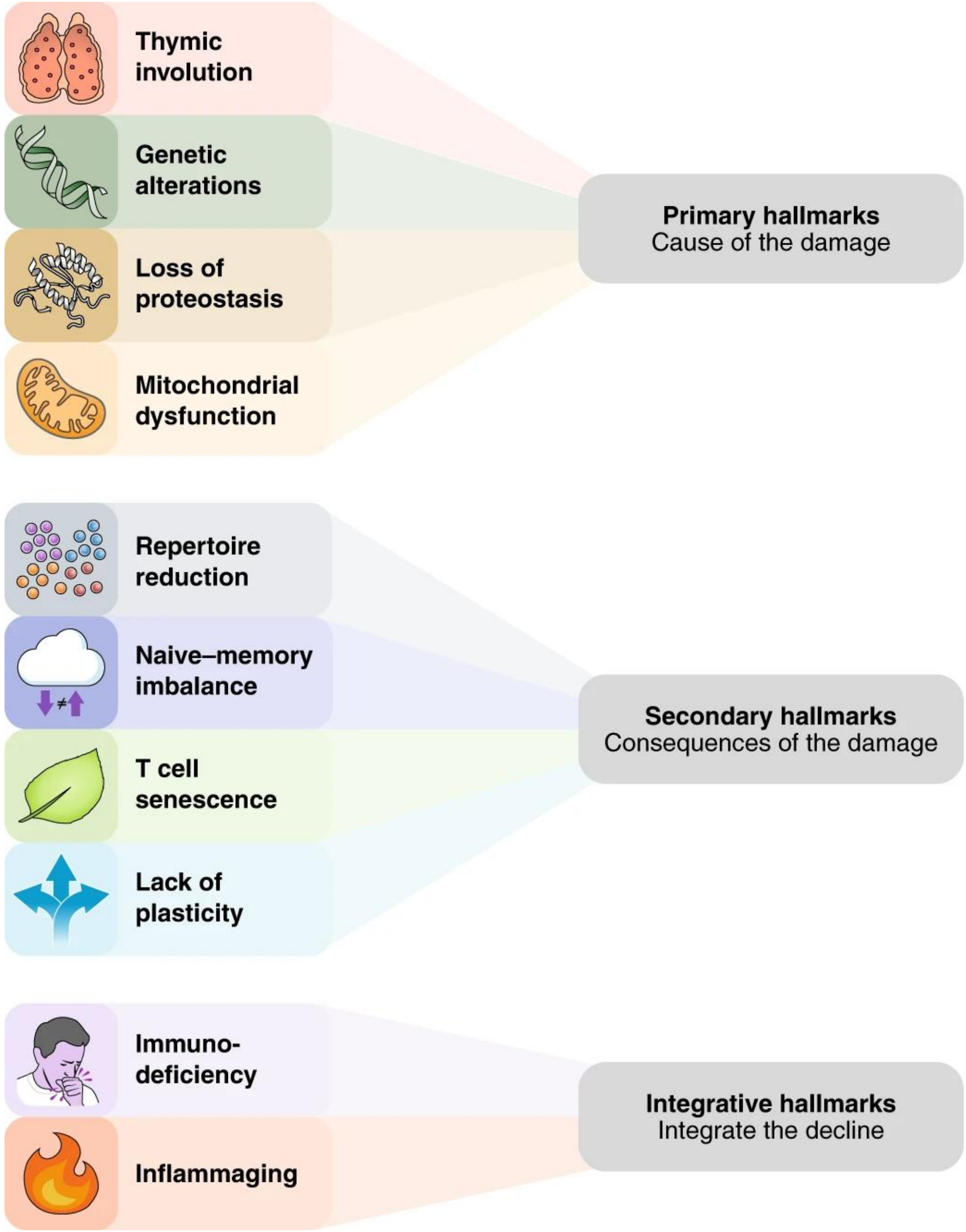
LETTER | Open Access

No increase of CD8+ TEMRA cells in the blood of healthy adults at high genetic risk of Alzheimer's disease

Laura Deecke, Jan Homann, David Goldeck, Olena Ohlei, Valerija Dobricic, Johanna Drewelies, Ilja Demuth, Graham Pawelec, Lars Bertram, Christina M. Lill

First published: 25 January 2024 | https://doi.org/10.1002/alz.13709



Hallmarks of T cells in aging

The hallmarks grouped into 3 categories, based on their hierarchical interconnections.

4 primary hallmarks account for the initial damage

- Thymic involution,
- Genetic and epigenetic alterations
- Loss of proteostasis
- Mitochondrial dysfunction

4 secondary hallmarks are consequences of primaries

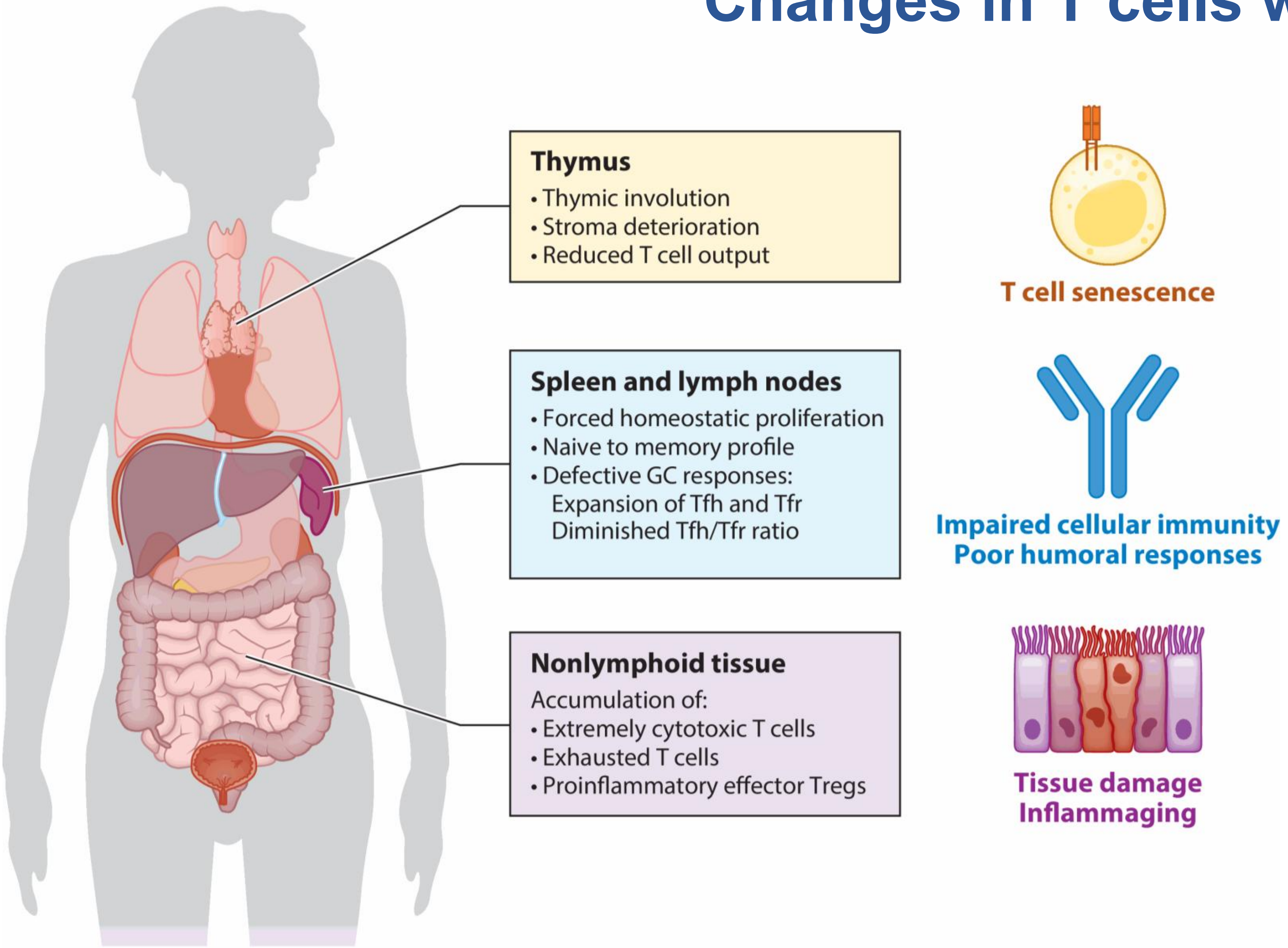
- Reduction of the TCR repertoire
- Expansion of the memory pool
- Lack of effector plasticity
- T cell senescence

2 integrative hallmarks are the consequences of the T cell functional deficiencies

- Immunodeficiency
- Inflammaging

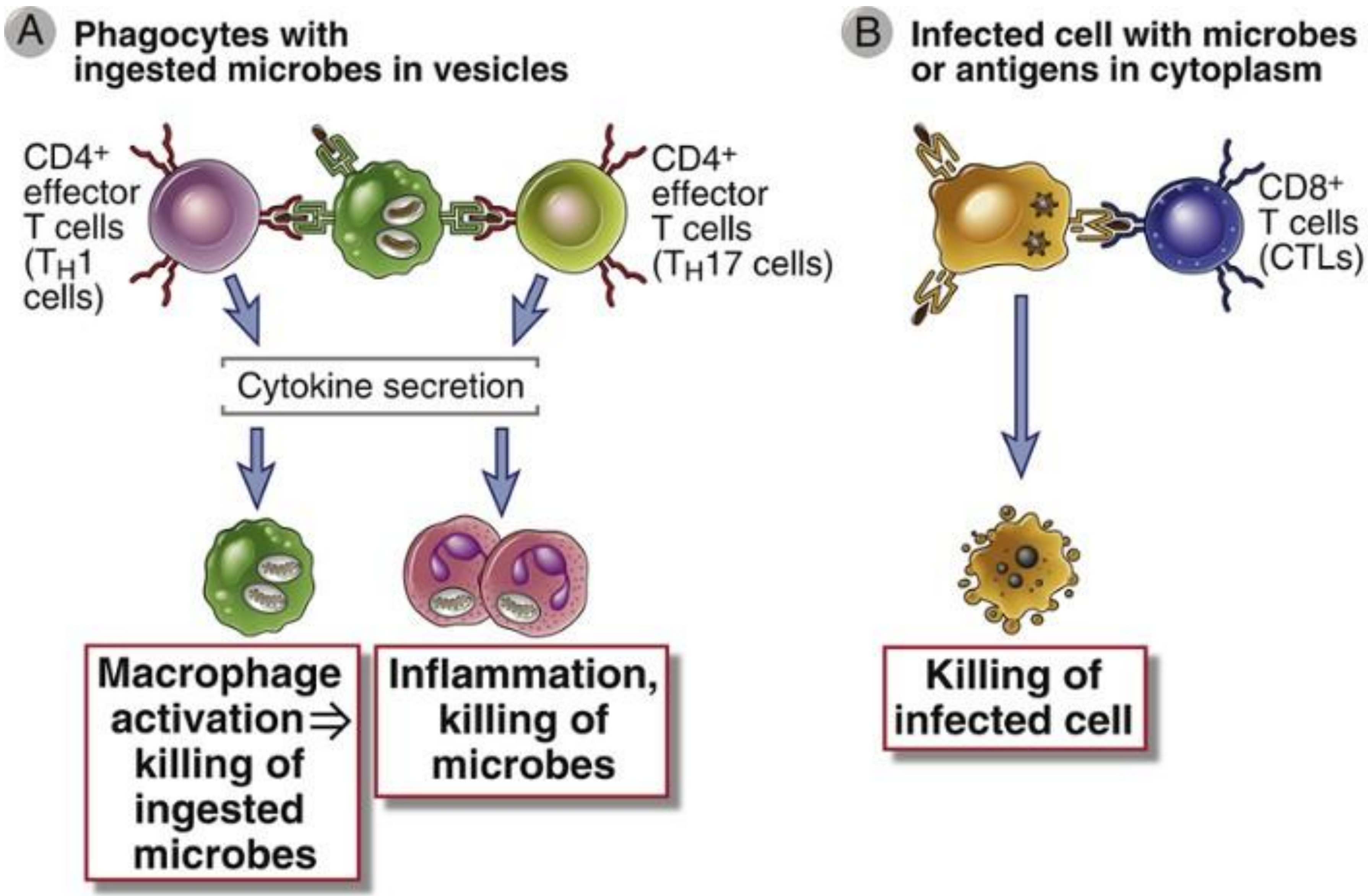
Mittelbrunn and Kroemer (2021) Hallmarks of T cell aging. Nat Immunol

Changes in T cells with aging

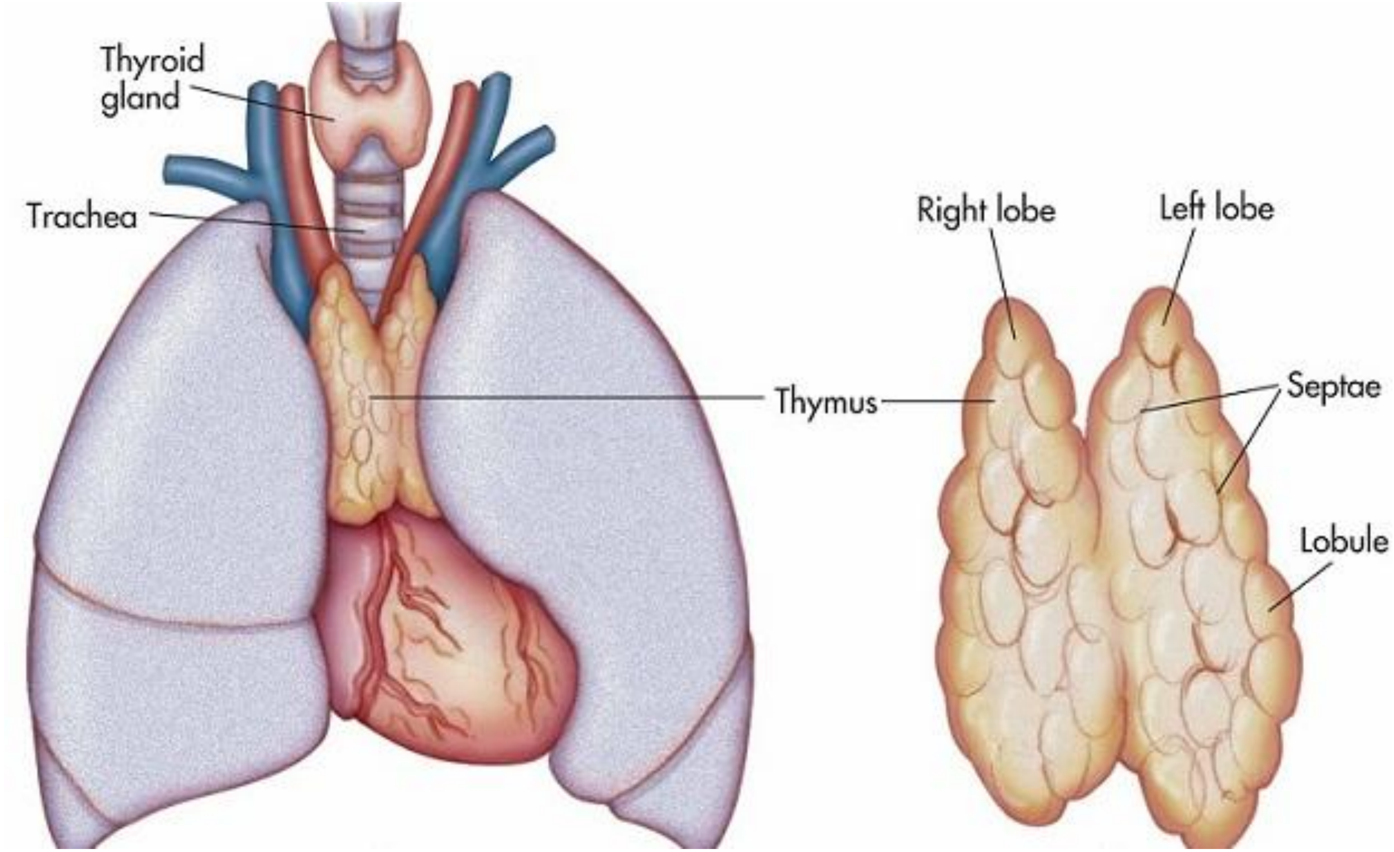


Soto-Heredero G, et al. 2023
Annu. Rev. Immunol. 41:181–205

CD4+ and CD8+ T cells have different effector functions

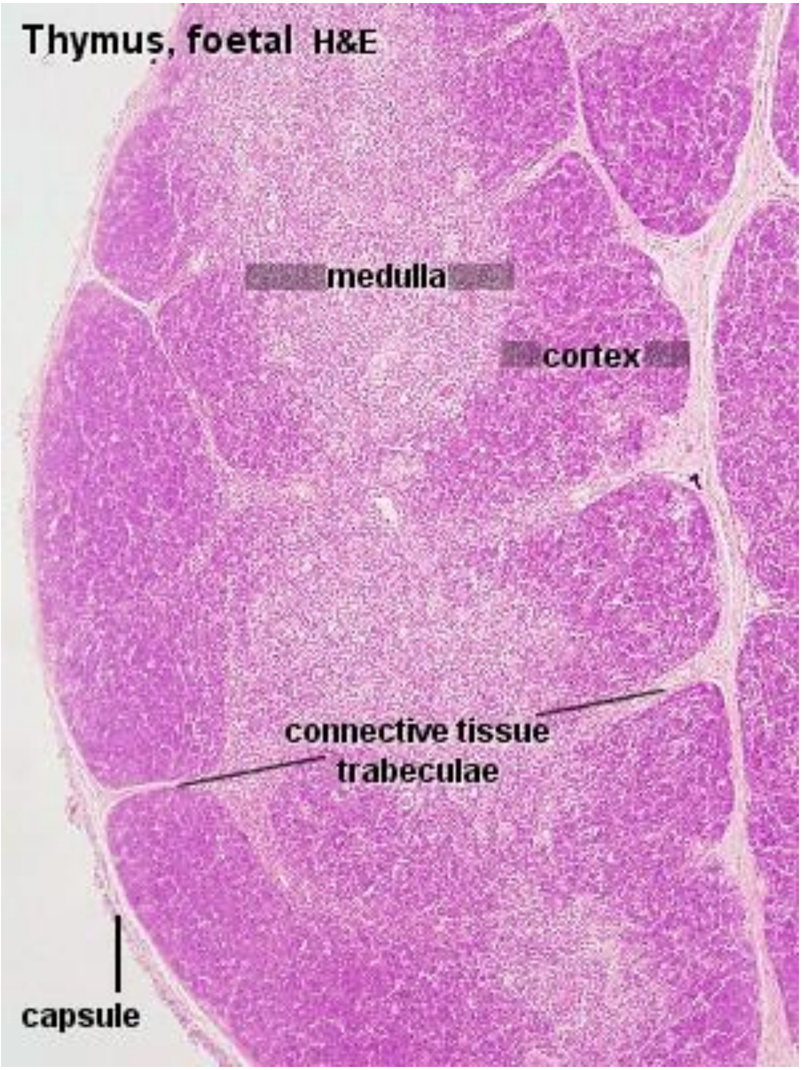


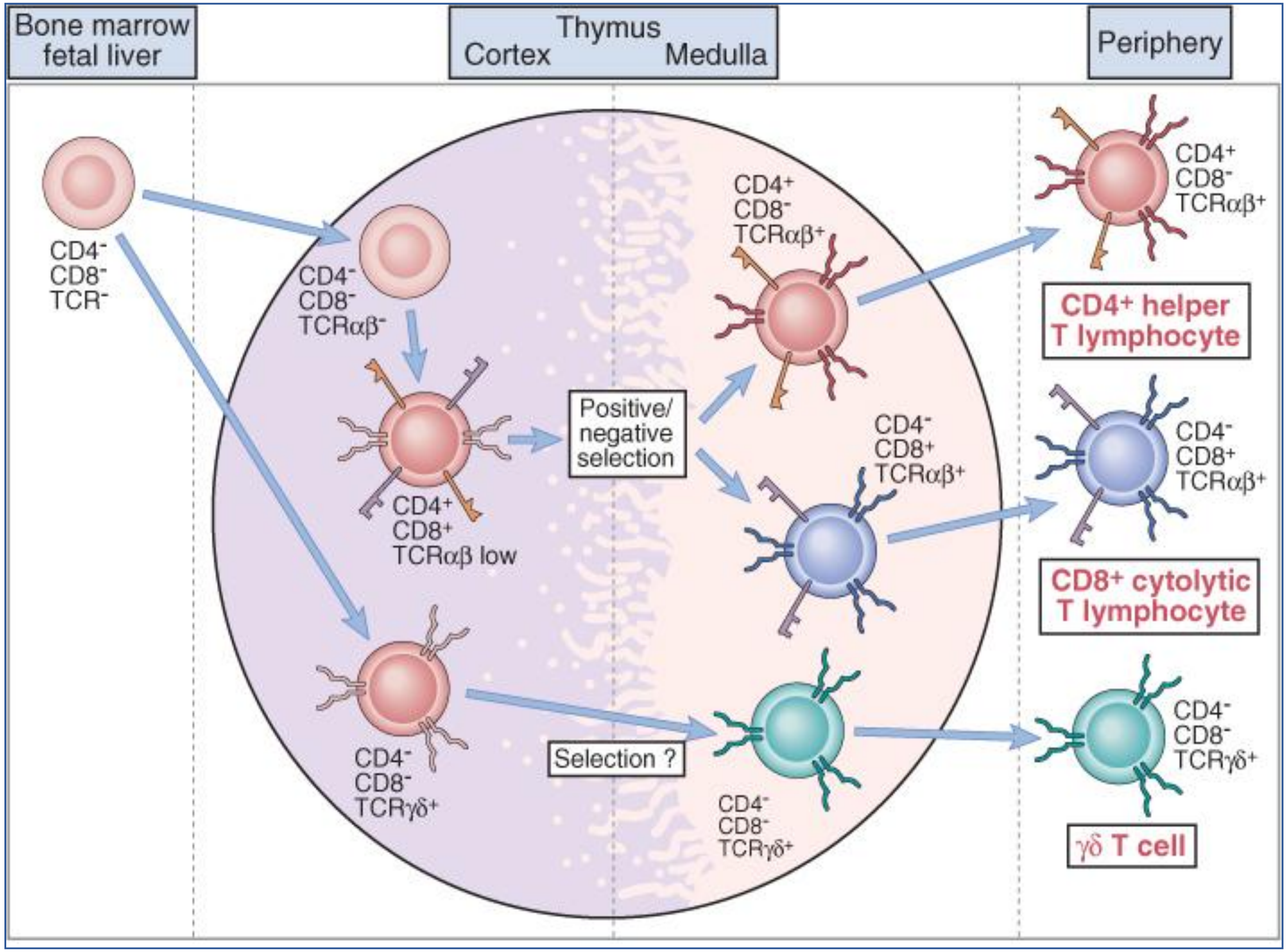
The thymus



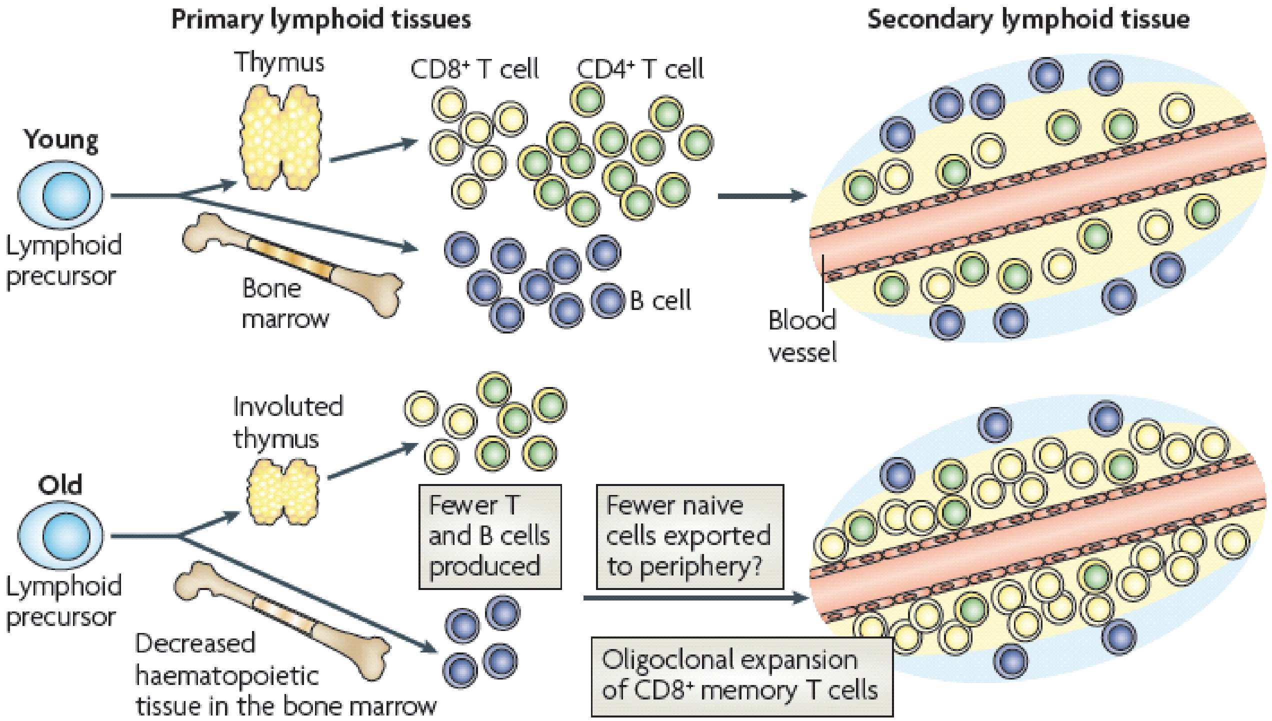
Thymus vulgaris

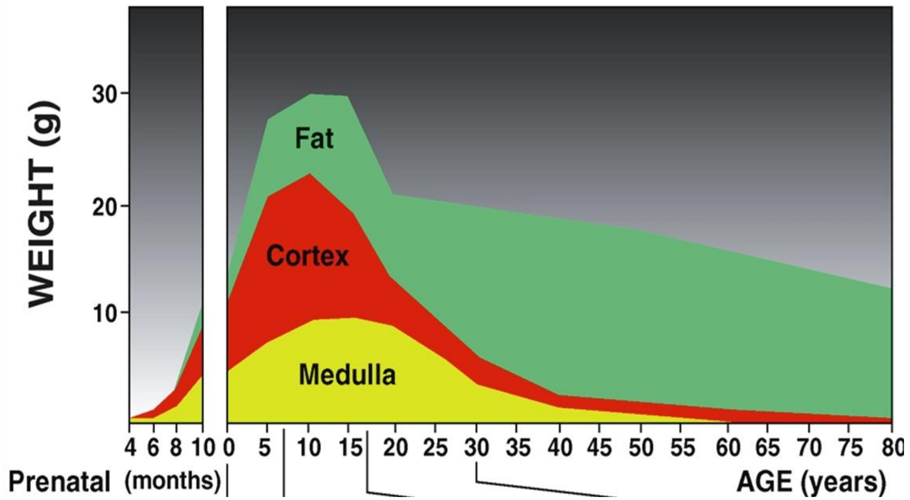
T cells differentiate in the thymus

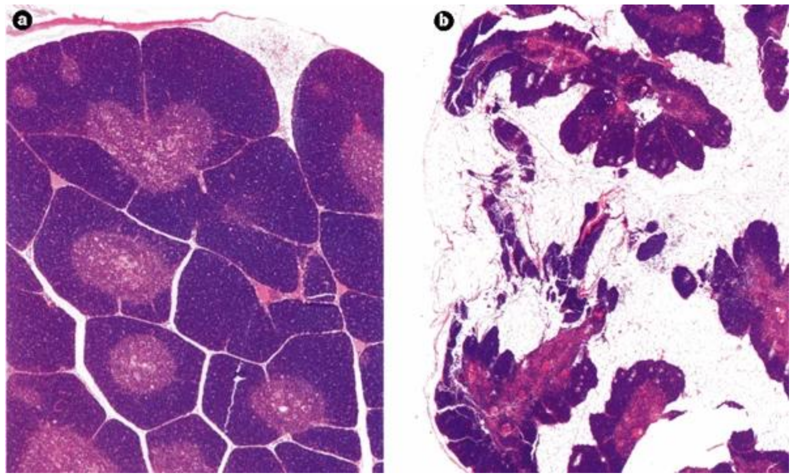




Age-related changes in the thymus



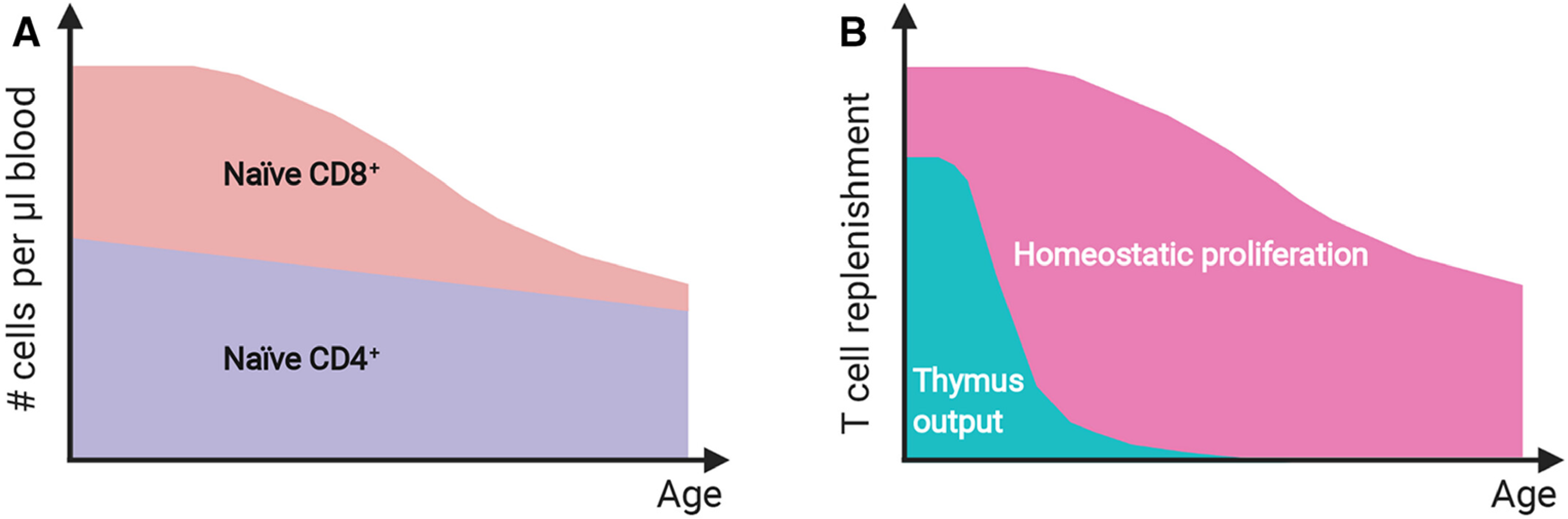




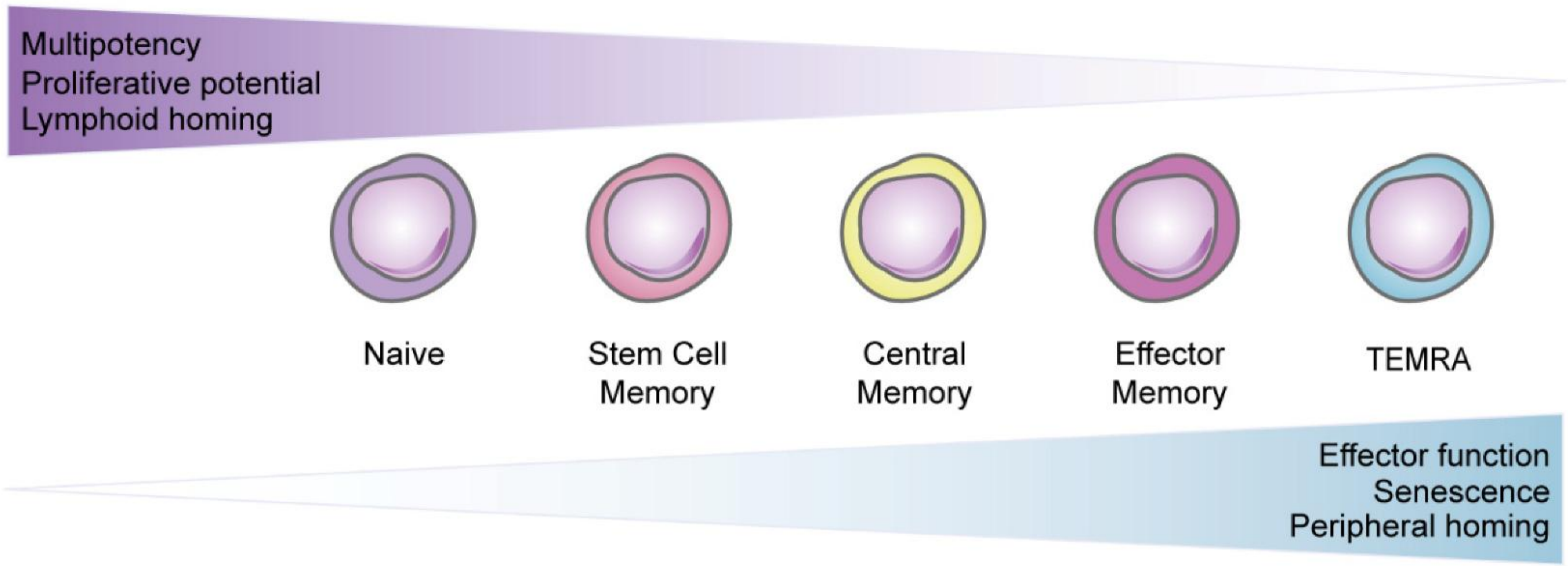
Young Old

- Thymus involutes and is replaced by adipose cells
- Less naïve T cells
- Oligoclonal expansion of T cells

Aging mostly impacts on the numbers of naive CD8+ T cells

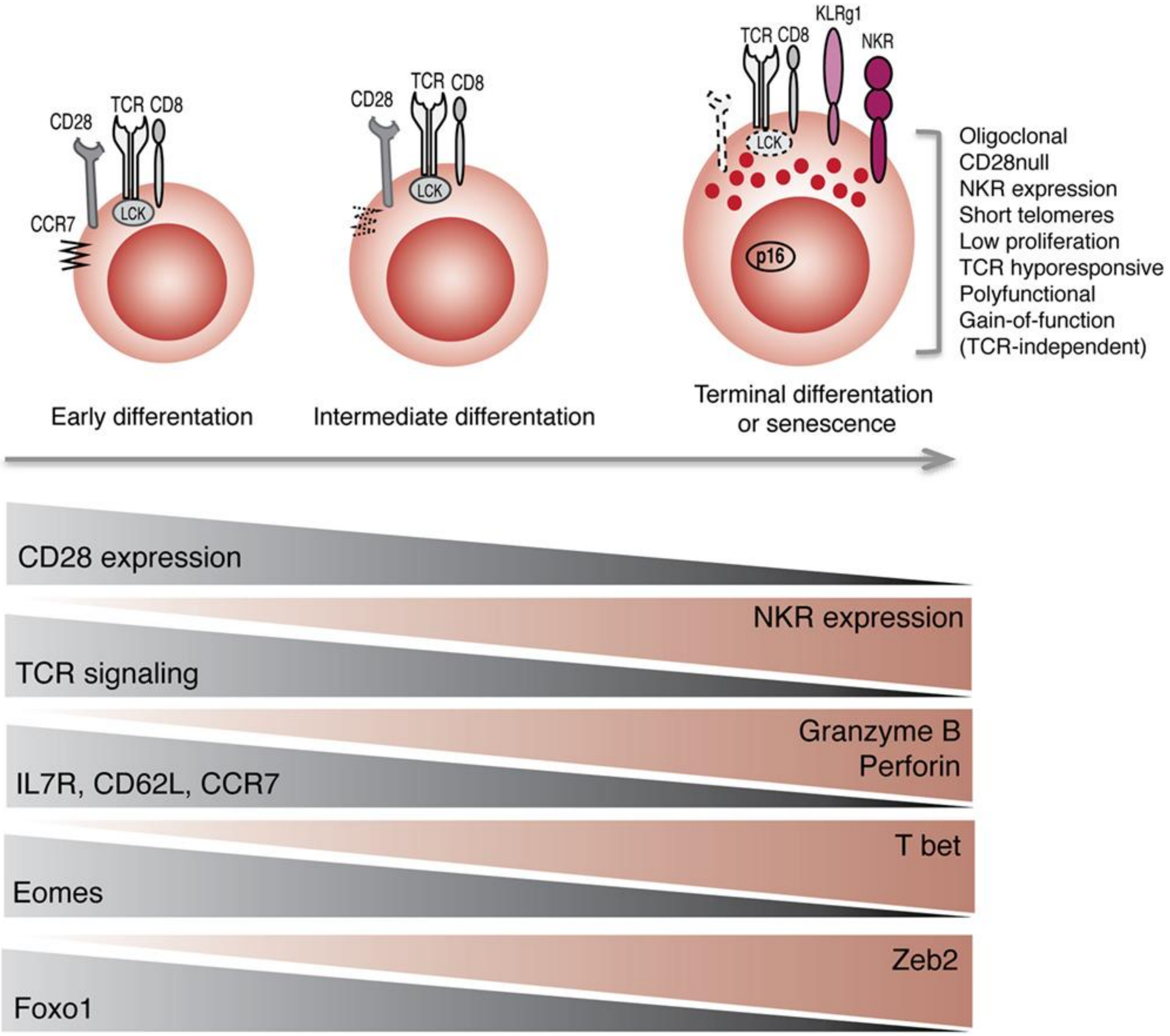


T cells differentiate from naïve to terminally differentiated T cells (TEMRA)



	Naive	Stem Cell Memory	Central Memory	Effector Memory	TEMRA
CD45RO	-	-	+	+	-
CD45RA	+	+	-	-	+
CCR7 (CD197)	+	+	+	-	-
CD62L (L-selectin)	+	+	+	-	-

Terminal differentiation of CD8+ T cells into NK-like T cells

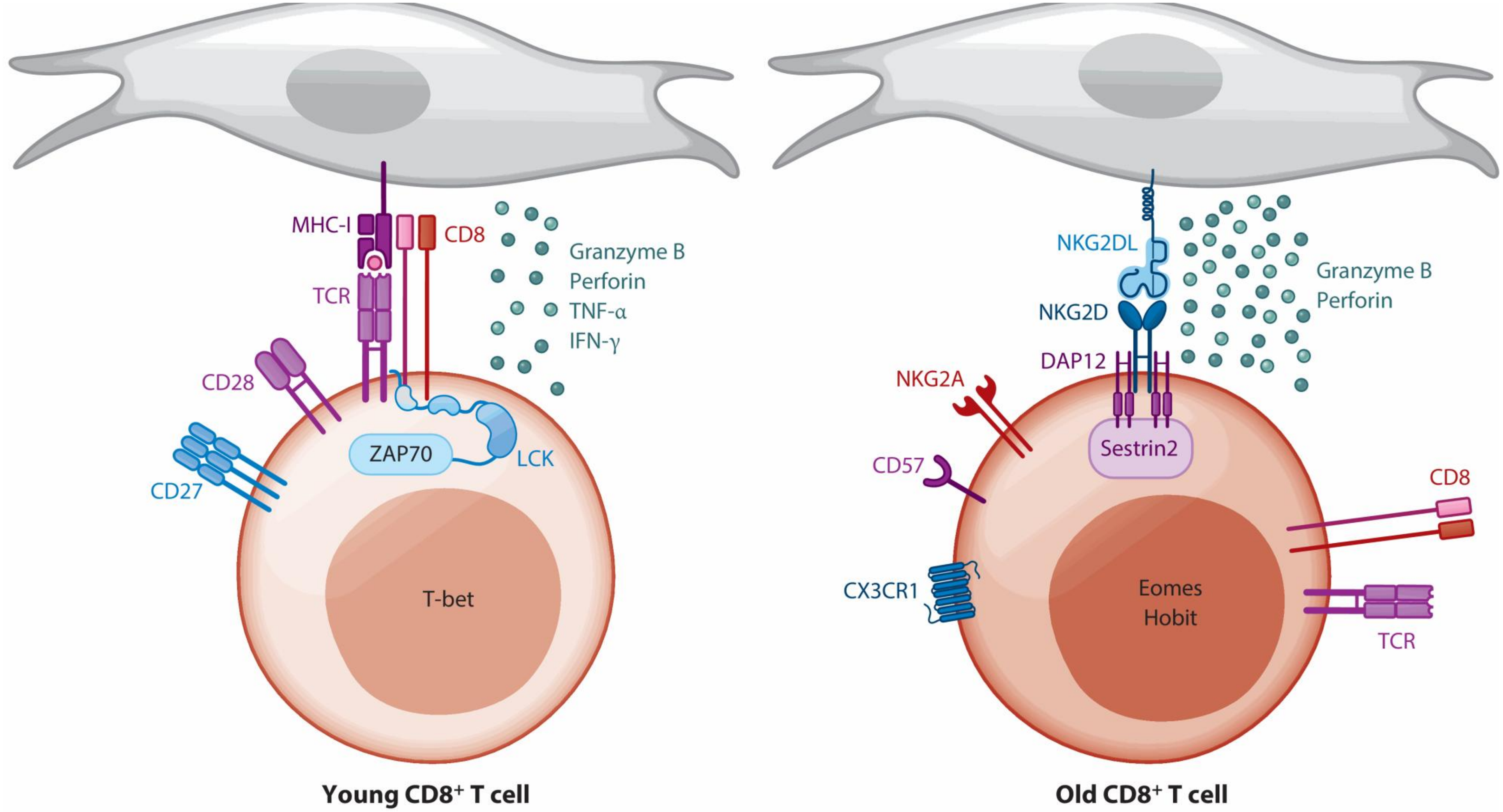


	Early differentiation	Intermediate differentiation	Terminal differentiation
Phenotypic markers			
CD28	++	+/−	−
CD27	++	+/−	−
CD45RA	++	+/−	+/−
CCR7	++	+	−
CD62L	++	+	−
CD57	−	+/−	++
KLRG1	−	+/−	++
Other NKR (KIR, NKG2, and CD56)	−	+/−	++
Functional features			
Proliferation	++	+	−
Telomerase activity	++	+	−
Telomeres	+++	++	+
Cytotoxicity	−	+	++
Cytokine secretion (TNF-α, IFN-γ)	−	+	++
Signaling pathways			
TCR signaling	+	++	+/−
IL-2 signaling	+	++	+/−
Pi3K–AKT–mTOR signaling	+	++	+/−
p38MAPK activation	−	−	+

KLRG1, killer cell lectin-like receptor G1; NKR, natural killer receptor; KIR, killer cell immunoglobulin-like receptor; NKG2, natural killer receptor G2, TNF-α, tumor necrosis factor alpha; IFN-γ, interferon gamma; PI3K, phosphatidylinositol-3 kinase; mTOR, mammalian target of rapamycin.

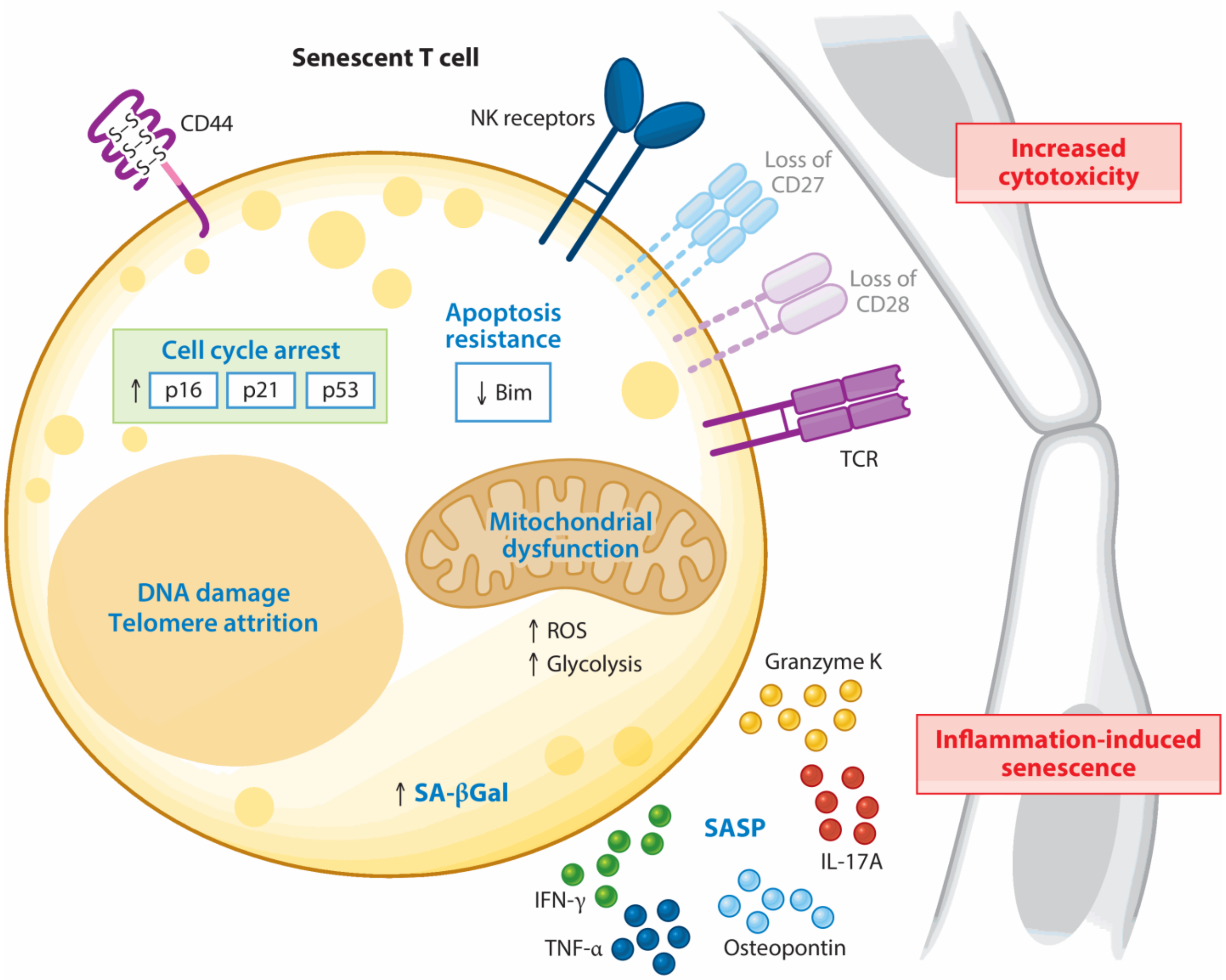
Pereira and Akbar 2016, Front Immunol

T cells in aged individuals loose costimulatory and activate NK cell markers



Soto-Heredero G, et al. 2023
Annu. Rev. Immunol. 41:181–205

Intracellular changes in T cells



Soto-Heredero G, et al. 2023
Annu. Rev. Immunol. 41:181–205

bioRxiv [Preprint]. 2025 Jun 14:2025.06.10.658841. doi: 10.1101/2025.06.10.658841.

Accumulation of SA-βGal-High Cells in Human Naïve T Cell Compartments Reveals a Stress-Adapted, Senescent-Like State

Andreea Cristina Alexandru [1], Genesis Vega Hormazabal [1], Hiroyuki Matsui [1], Herbert Kasler [1], Sierra Lore [1], Carlos Galicia Aguirre [1], Andrea Roberts [1], Indra John Heckenbach [2], Ritesh Tiwari [1], Ryan Kwok [1], Sydney Becker [3], Eric Verdin [4]

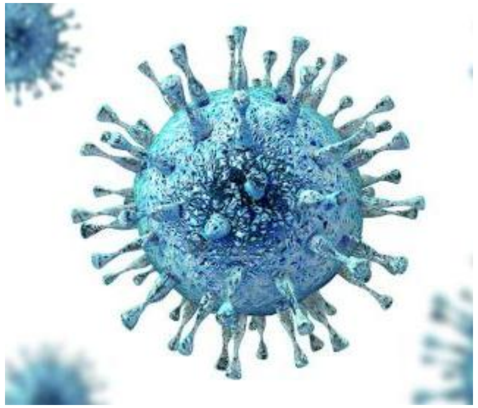
Affiliations + expand

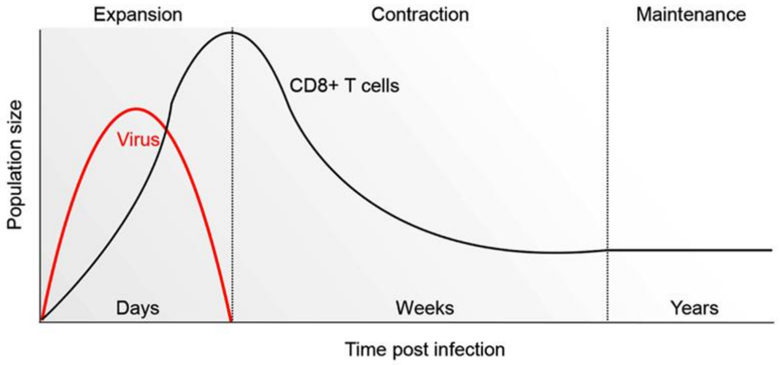
PMID: 40661537 PMCID: PMC12259081 DOI: 10.1101/2025.06.10.658841

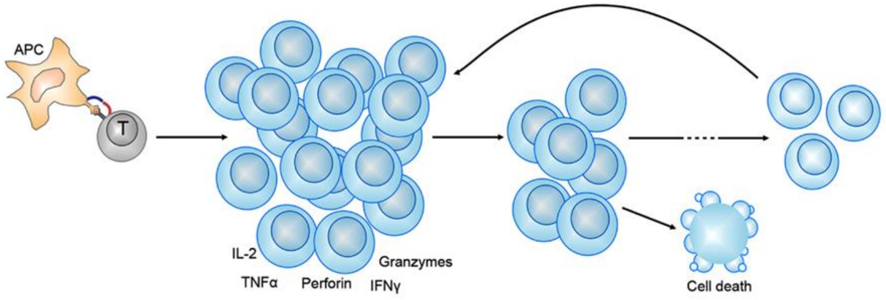
Abstract

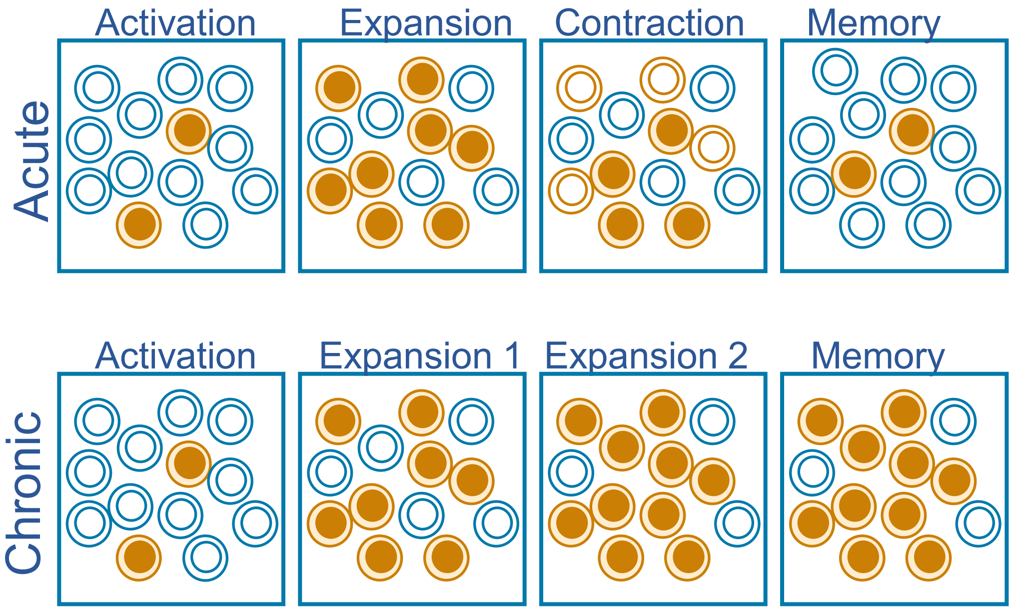
Aging is associated with a decline in immune function termed immunosenescence, characterized by accumulation of senescent-like immune cells and chronic inflammation, known as inflammaging. While senescence-associated β-galactosidase (SA-βGal) activity is a well-established senescence marker, its functional significance and the precise cellular subsets affected within the T cell compartment remain unclear. Here, we identify and characterize a previously unrecognized subset of naïve $CD4^+$ and $CD8^+$ T cells displaying high SA-βGal activity that significantly increases with age. Despite exhibiting hallmark features of senescence such as DNA damage, nuclear envelope disruption, loss of heterochromatin, and pronounced dysregulation of autophagy and lysosomal pathways, these SA-βGal-high naïve T cells notably lack the canonical senescence marker p21CIP1 and retain robust proliferative capacity upon activation. Remarkably, naïve $CD4^+$ SA-βGal-high T cells acquire cytotoxic properties including NK-like features, granzyme secretion, and the ability to induce paracrine DNA damage in endothelial cells. Mechanistically, we demonstrate that impaired autophagic flux contributes significantly to this phenotype. Our findings address critical knowledge gaps regarding the nature and functional plasticity of senescence-like states in naïve T cells, highlighting a novel link between lysosomal-autophagic dysfunction, cellular stress adaptation, and inflammaging. Understanding this unique T cell population provides important insights into immune aging and offers potential targets to mitigate age-associated immune dysfunction and chronic inflammation.

Cytomegalovirus (CMV) chronic infection associates with the accumulation of terminally differentiated T cells









Age-related changes in gene expression of PBLs

A study of 15,000 people showed changes in the expression of 1500 genes, many of them related to immune functions

nature COMMUNICATIONS

ARTICLE

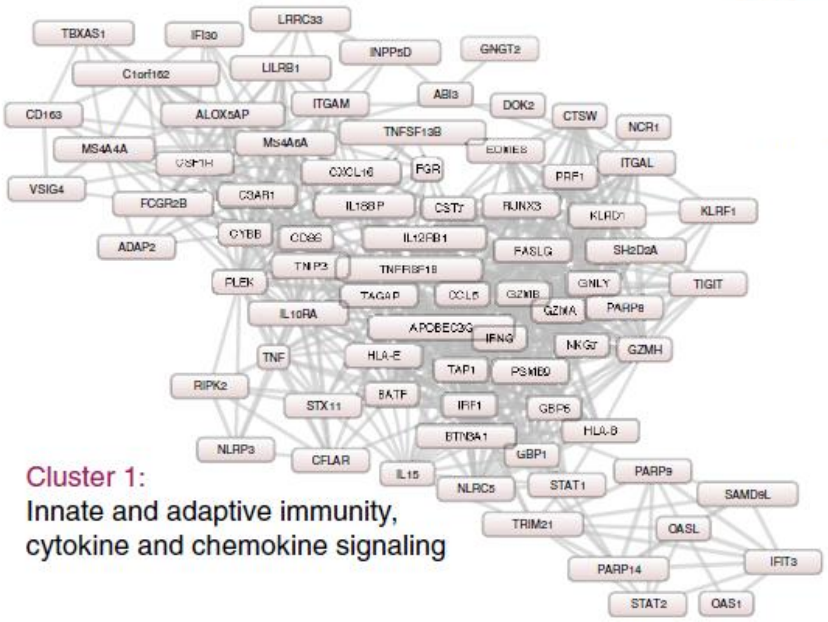
Received 16 Jan 2015 | Accepted 7 Sep 2015 | Published 22 Oct 2015

DOI: 10.1038/ncomms9570

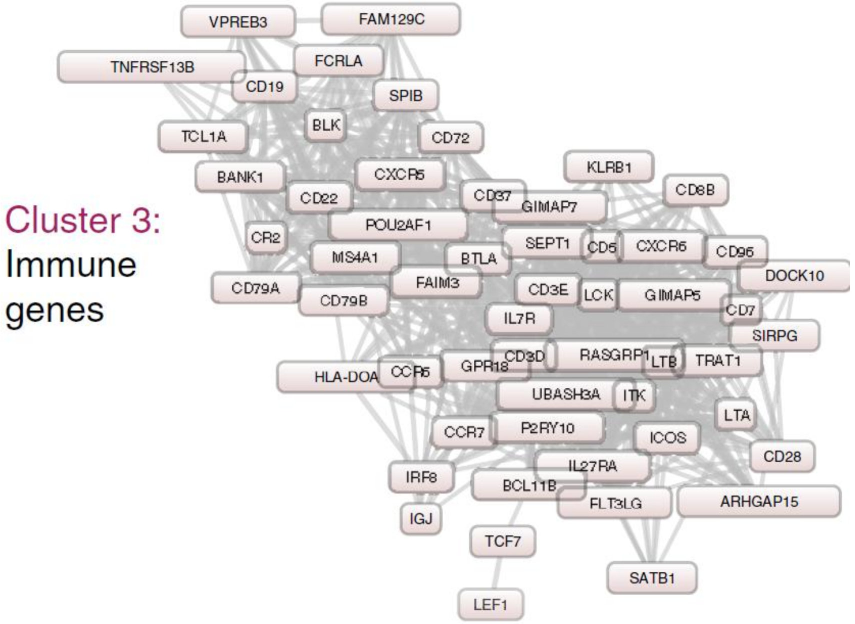
The transcriptional landscape of age in human peripheral blood

Marjolein J. Peters et al.#

Upregulated immune genes

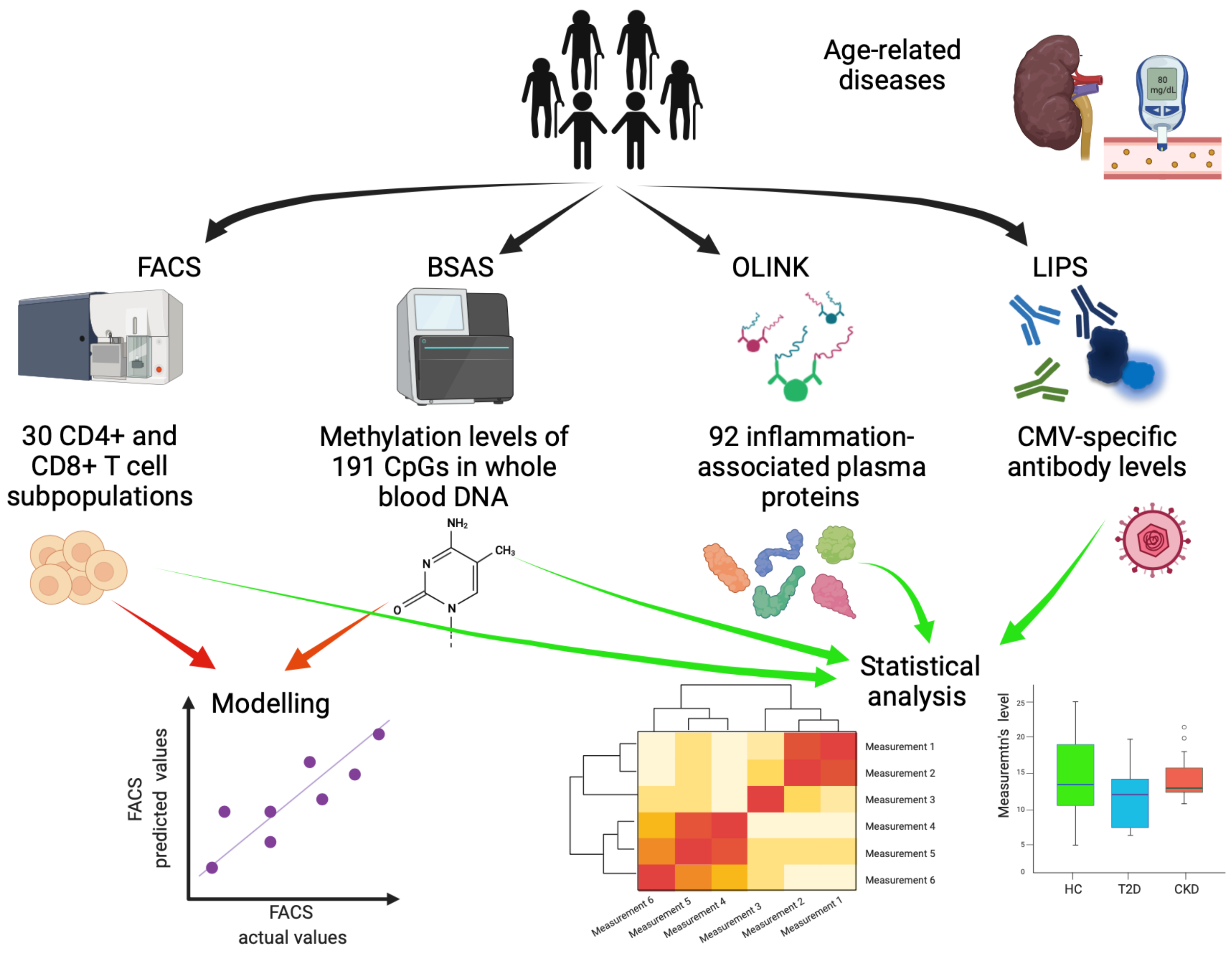


Downregulated immune genes



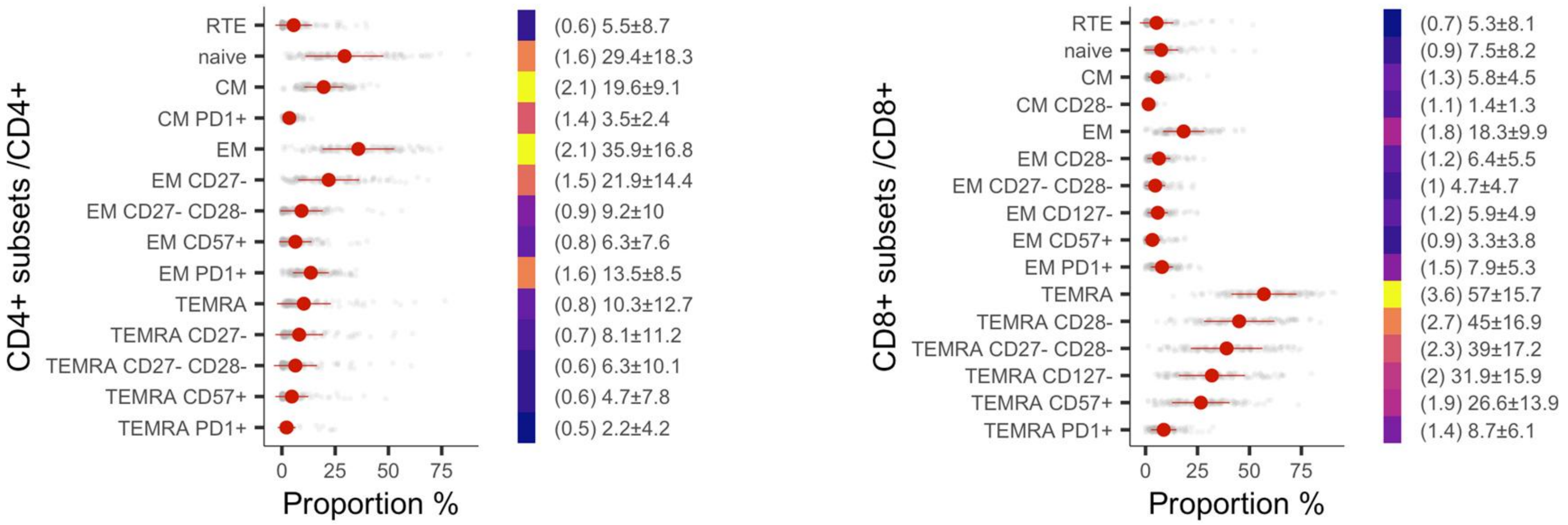
Peters et al. 2015 Nat Comm

T cell profiling in old individuals (140 persons over 65 years)



Salumets et al 2022, Aging Cell

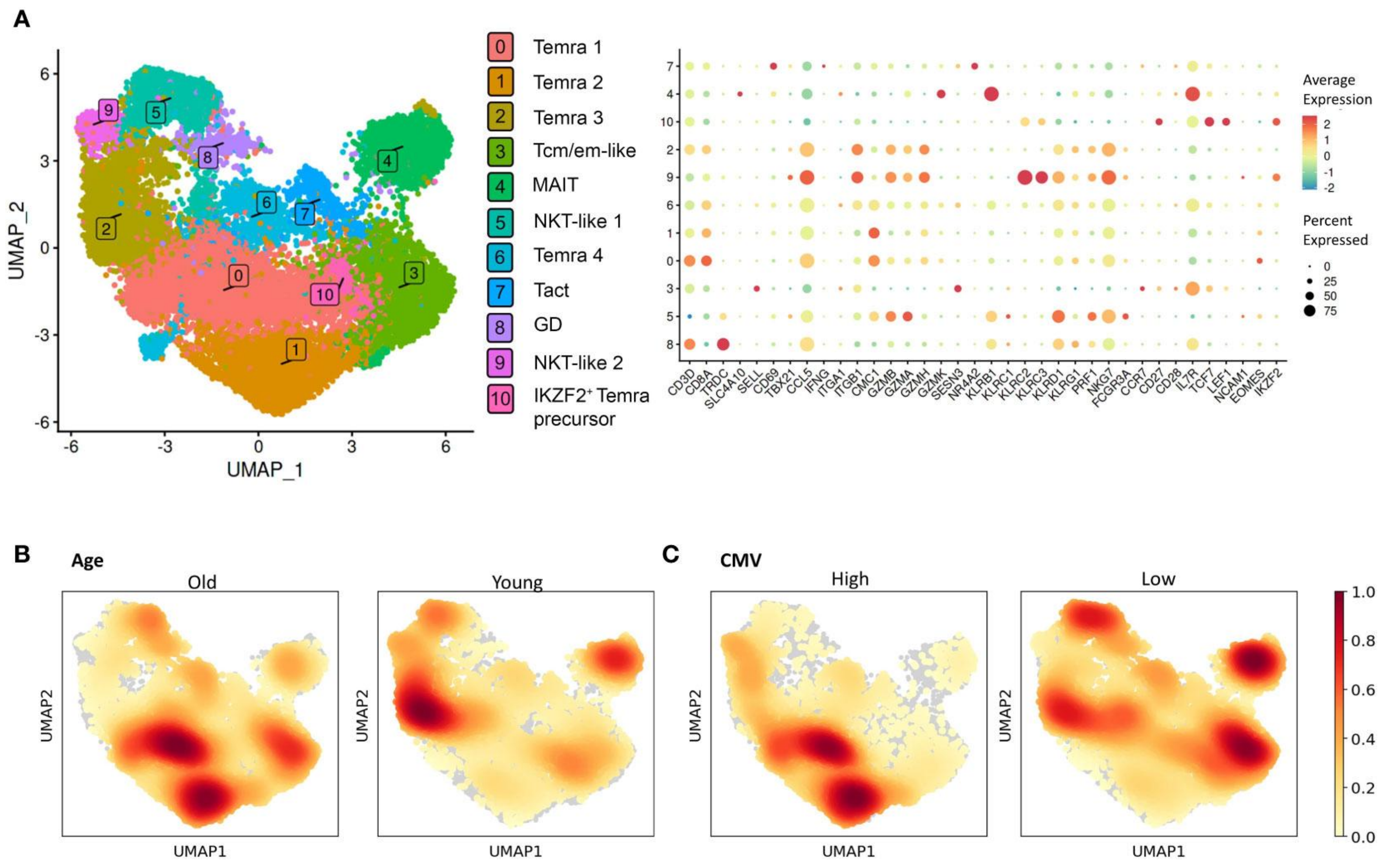
Large and variable CD8+ TEMRA populations in old people



Salumets et al 2022, Aging Cell

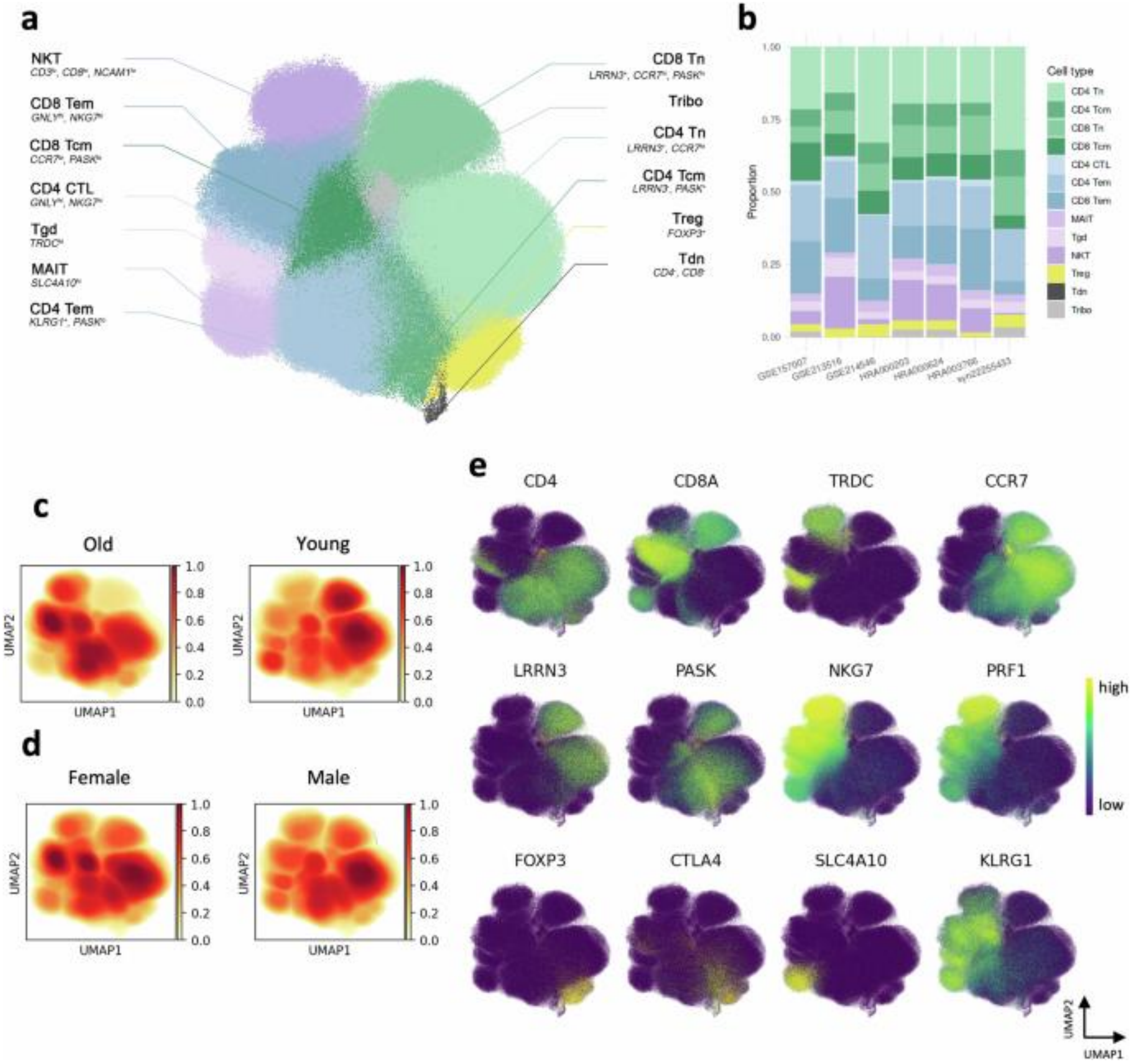
Two CD8+ TEMRA cell subpopulations in old individuals

- Sorted CCR7^{lo} CD45RA^{hi} CD8+ TEMRA cells are heterogenous
- Five populations corresponding to CD8+ TEMRA cell subpopulations
  - Cluster 0: TEMRA1
  - Cluster 1: TEMRA2
  - Cluster 2: TEMRA3
  - Cluster 6: TEMRA4
  - Cluster 10: IKZF+ TEMRA precursor
- CD8+ TEMRA1 and 2 enriched in old and CMV^{+} individuals
- CD8+ TEMRA1 and 2 express CMC1 and EOMES, high CD8A
- Compared to TEMRA3 and NKT –like cells TEMRA1 and 2 are lower in cytotoxic markers



Türk et al. 2024 Front Immunol

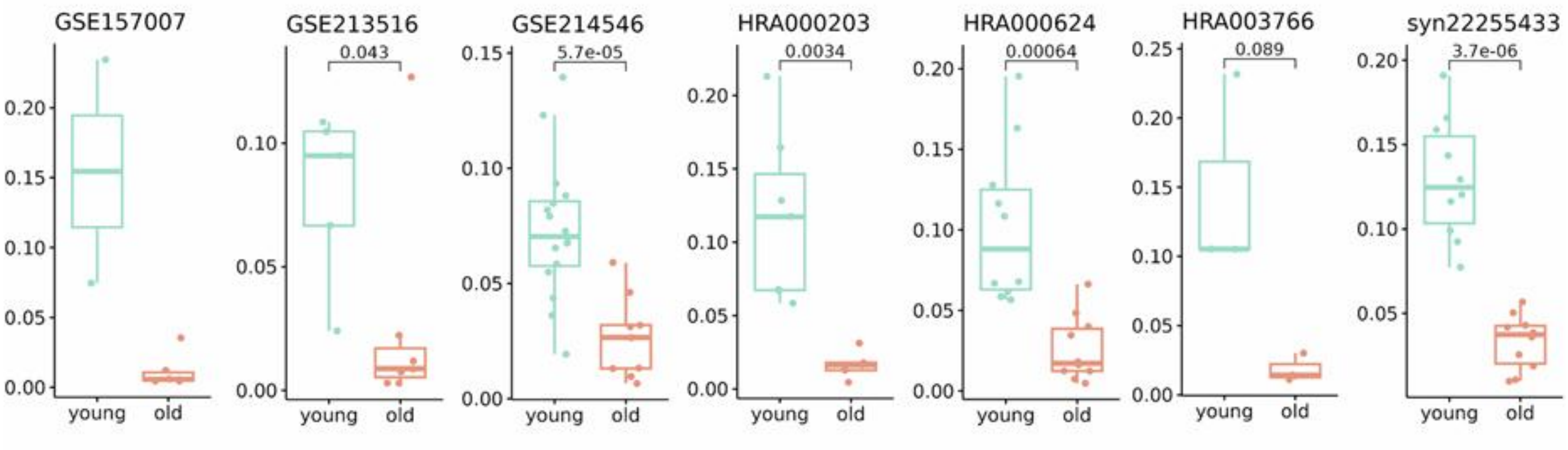
Integrating data on T cells from seven scRNAseq studies



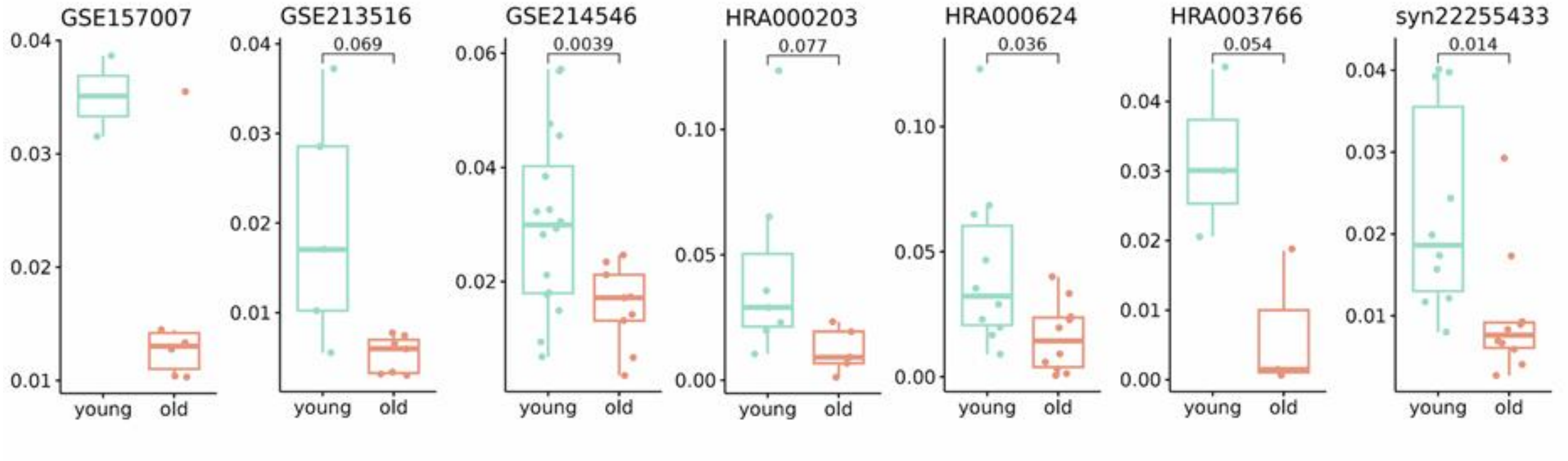
Filippov et al 2024. An integrated single-cell atlas of blood immune cells in aging. NPJ Aging.

CD8+ T cells and MAIT cells are most consistently declining with age

CD8 naïve cells

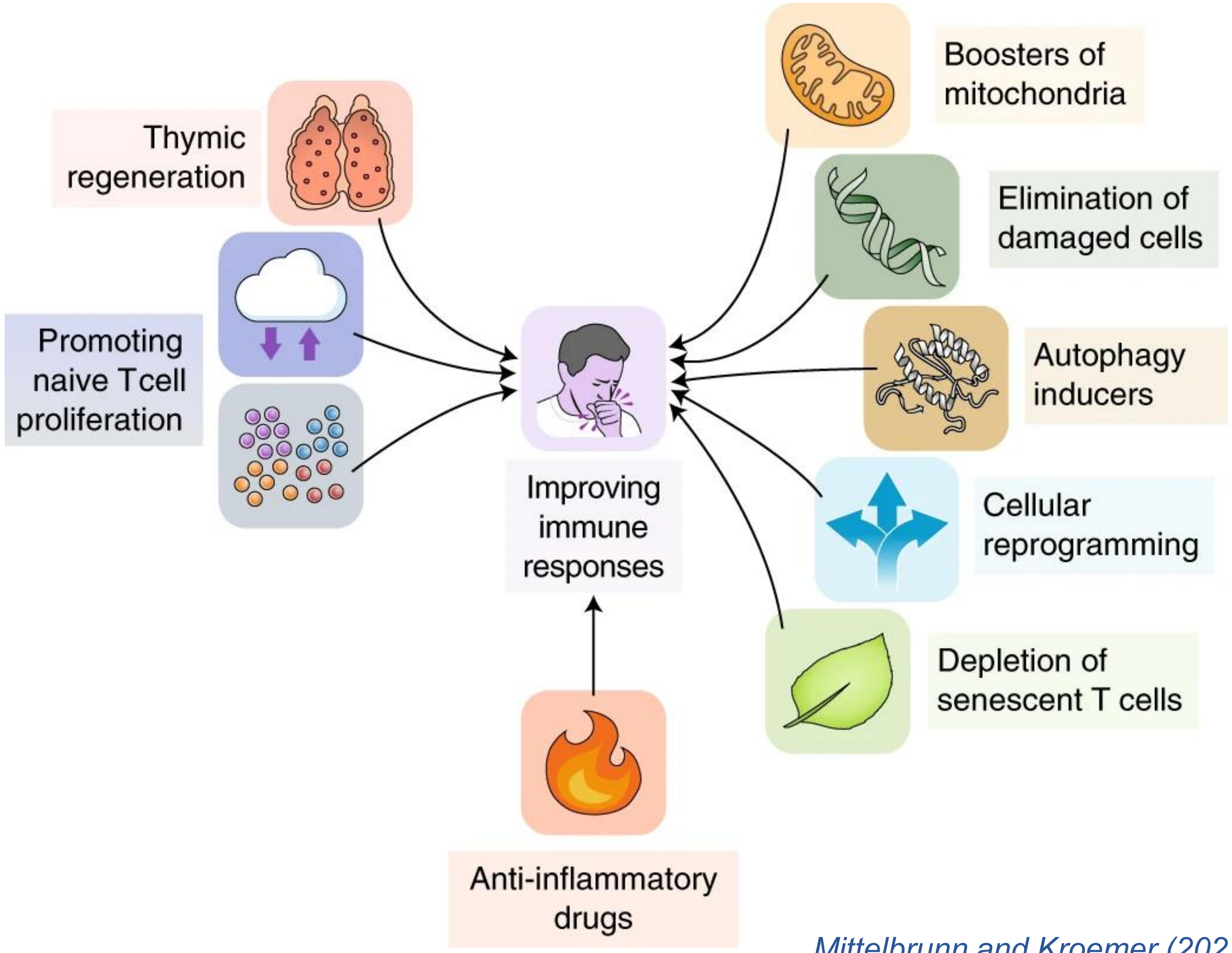


MAIT cells



Filippov et al 2024. NPJ Aging.

The interventions we should focus on to improve our immune responses



Mittelbrunn and Kroemer (2021) Hallmarks of T cell aging. Nat Immunol

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Thank you!

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