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Paestum (SA) 15-17 maggio 2014

Invecchiamento e infezioni:

non solo una questione di tempo trascorso

Prof. Roberto Paganelli

Dipartimento di Medicina e Scienze dell'invecchiamento

Università "G. D'Annunzio" di Chieti - Pescara

Disclosure

In relation to this presentation, I declare that there are no conflicts of interest.

A conflict of interest is any situation in which a speaker or immediate family members have interests, and those may cause a conflict with the current presentation. Conflicts of interest do not preclude the delivery of the talk, but should be explicitly declared. These may include financial interests (eg. owning stocks of a related company, having received honoraria, consultancy fees), research interests (research support by grants or otherwise), organisational interests and gifts.

Cosa c'era prima e ancora oggi

Il mio Maestro in Medicina

Studi sulla Immunosenescenza

- Partecipante al gruppo europeo ImAginE e progetto del 5 FP – ultima riunione decennale 2012 Tubingen, rapporto pubblicato su AGE – membro del gruppo Link-age 2008-2011
- Collaborazione istituzionale con Miller School of Medicine di U. of Miami con 1 dottorato internazionale – studio su vaccinazione per H1N1 in anziani sani, T2D e AR (fine 2013, tesi 2014)
- Gruppo di studio della SIAAIC su Allergia, Asma e Invecchiamento

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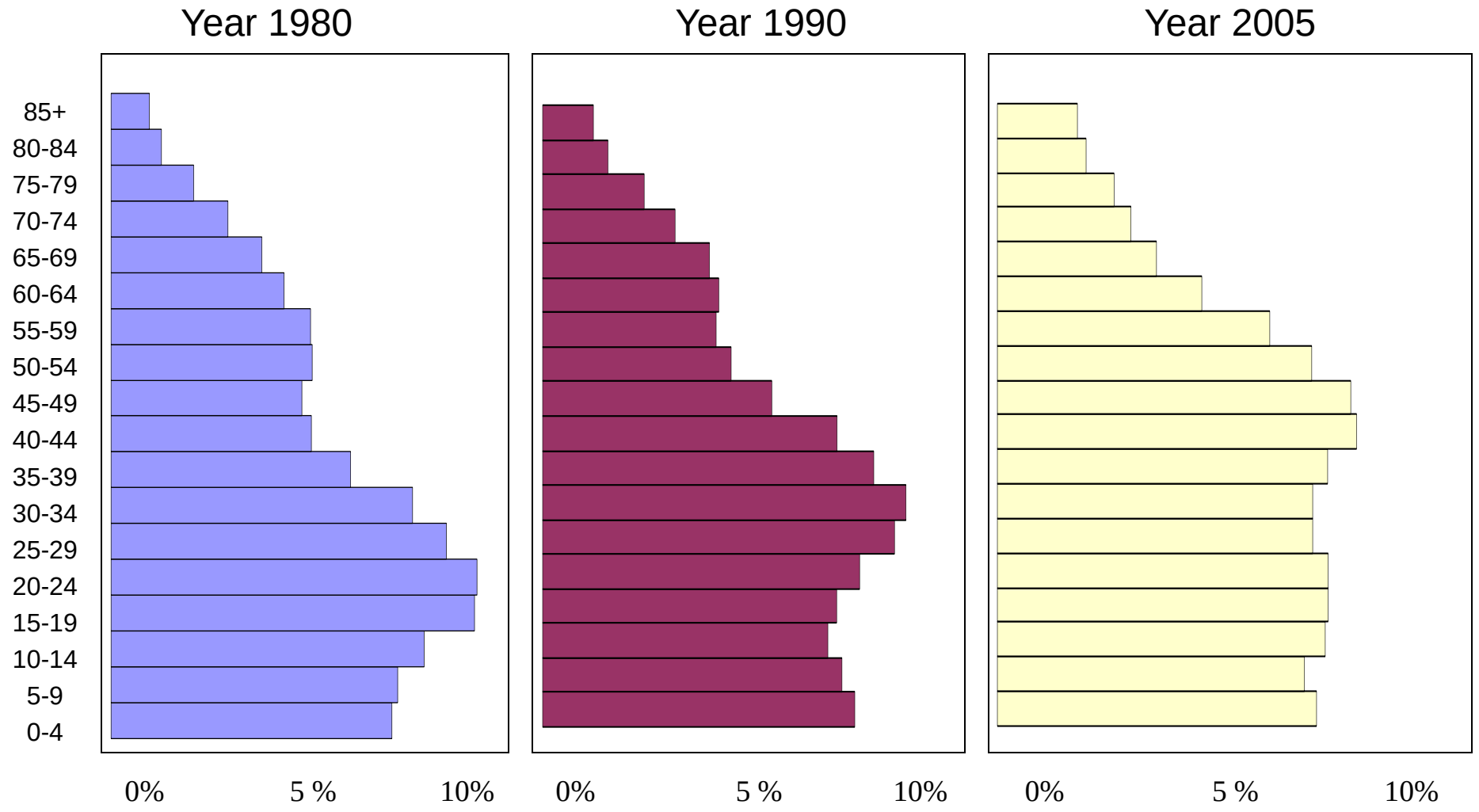
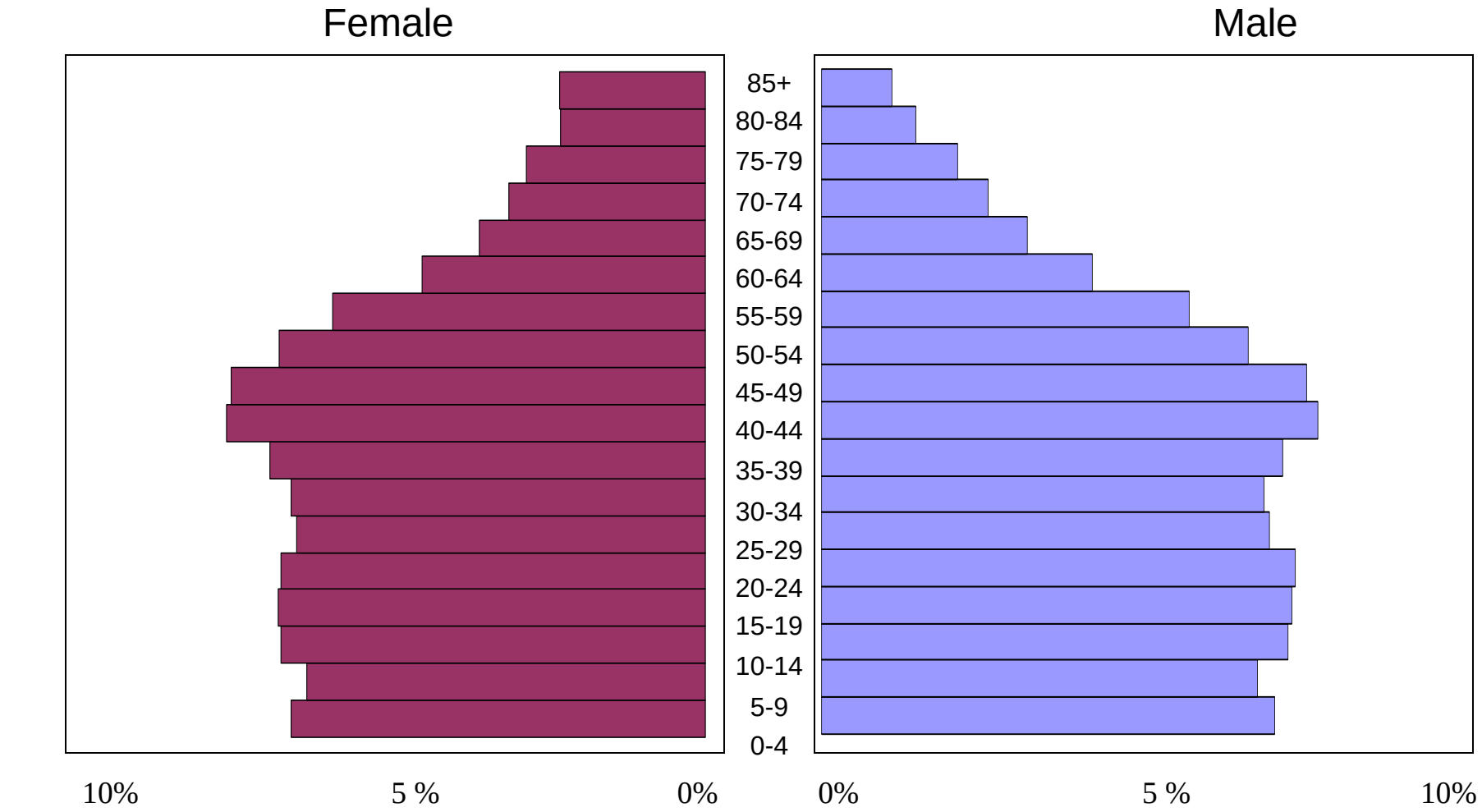
Age Distribution of U.S. Population, 1980, 1990, and 2005

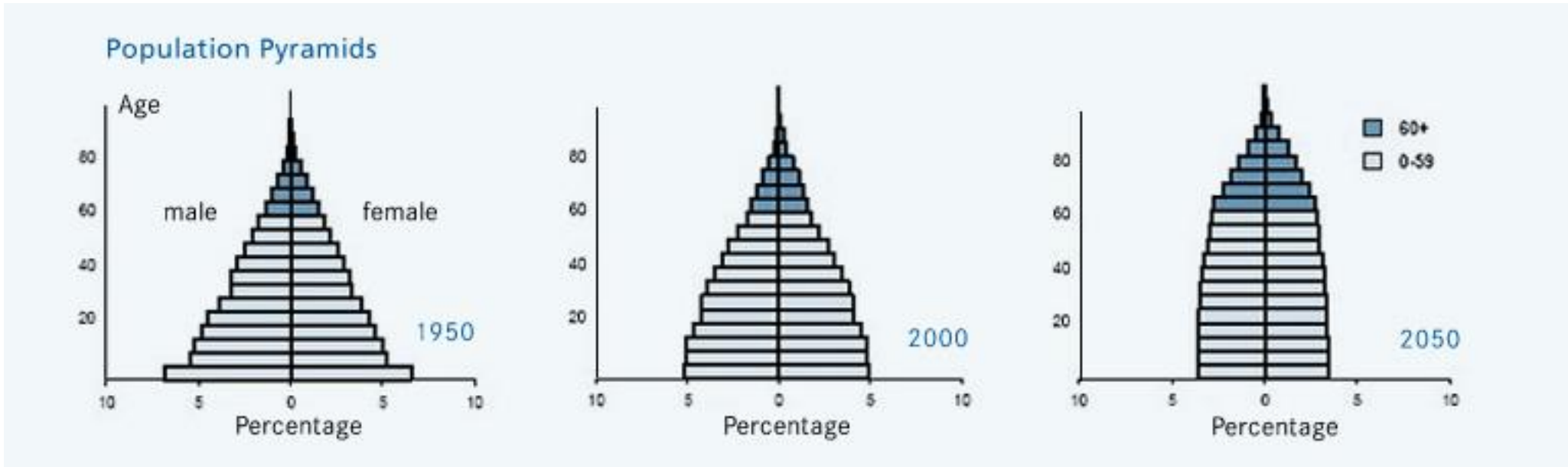


Data source: The Bureau of the Census

Age Distribution of U.S. Population by Sex, 2005



Data source: The Bureau of the Census


Population Pyramids
Age
male
female
1950
2000
2050
60+
0-59
80
60
40
20
10
5
0
5
10
Percentage

Invecchiamento

- **Inizia alla nascita; è un fenomeno inevitabile**
- **Influenza vari sistemi (p.es. sistema nervoso, sistema immunitario, endocrino, riproduttivo)**
- **Comporta perdita di funzioni accompagnata da una bassa fertilità**
- **Per senescenza si intende qualcosa di diverso**

Table 1. Glossary of definitions and terms.

ageing	a decline in an organism's fertility or survival though time
apoptosis	cell death induced by molecular mechanism of ageing
evolutionary stable	strategy uninvadable by any other
fitness	a measure of the spread of gene into future generations
free radicals	the reactive by-products of cellular metabolism
gene environment effect	genotypes respond differently in different environments
gerontology	the study of ageing
hazard of mortality	probability of dying within an interval of time
lifespan	the period of life from birth until death
pleiotropy	the multiple phenotypic effects of a gene
population dynamics	change in the size of the population through time
senescence	a progressive increase in the age-specific death rate (also see *ageing*)
trade-off	constraints on resource allocation patterns
statistical distribution	number of times each possible outcome occurs in a number of trials

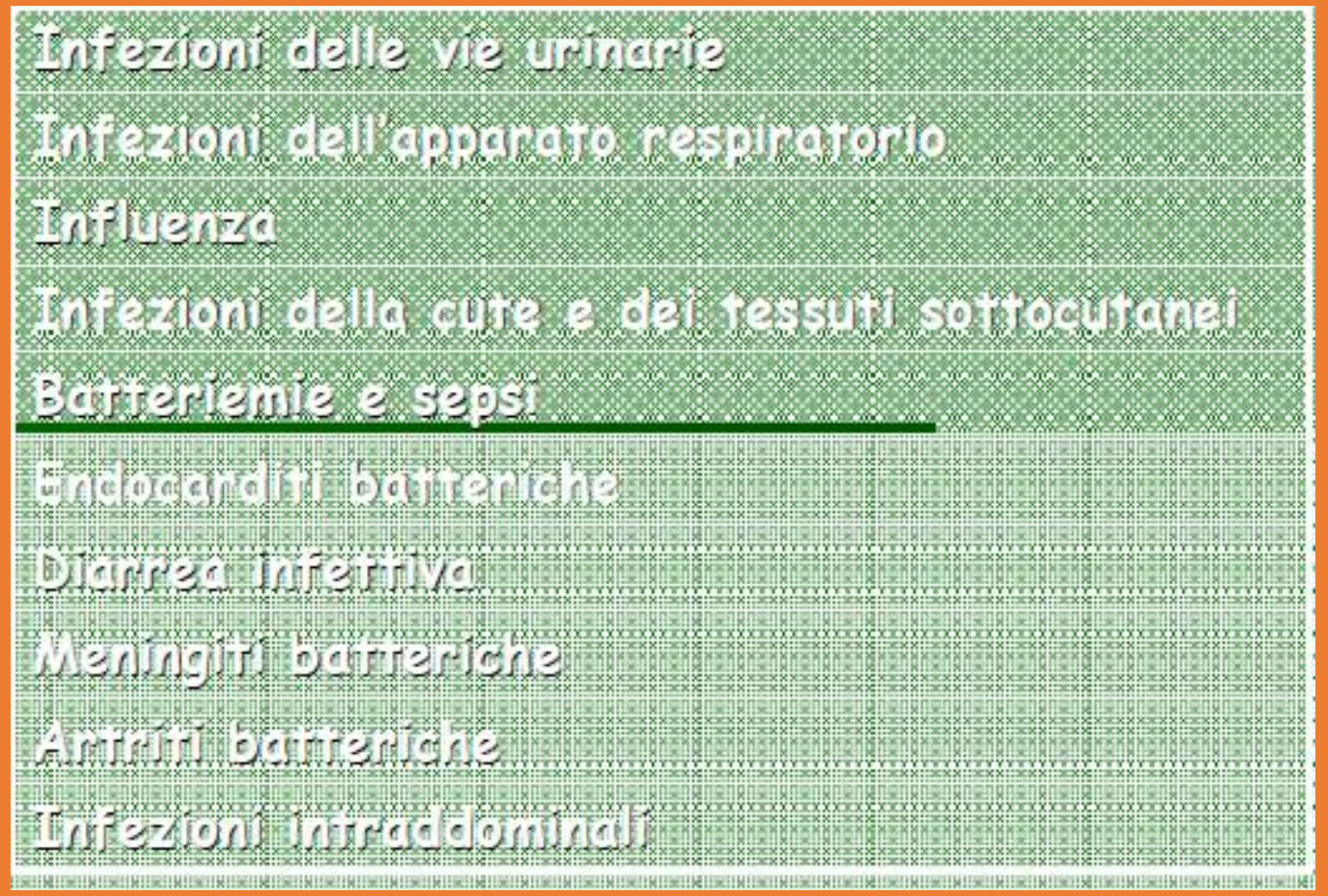
- Influenza del controllo genetico sulla velocità con cui si invecchia…

While no single gene can be credited as responsible for ageing, the mechanisms of ageing are clearly under genetic control. The molecular, cellular and physiological aspects of ageing involve various forms of damage to DNA, cells, tissues and organs. This so called 'free radical theory of ageing', originally conceived by Harman (1956), provides a central theme in the biology of ageing. Harman (1956)

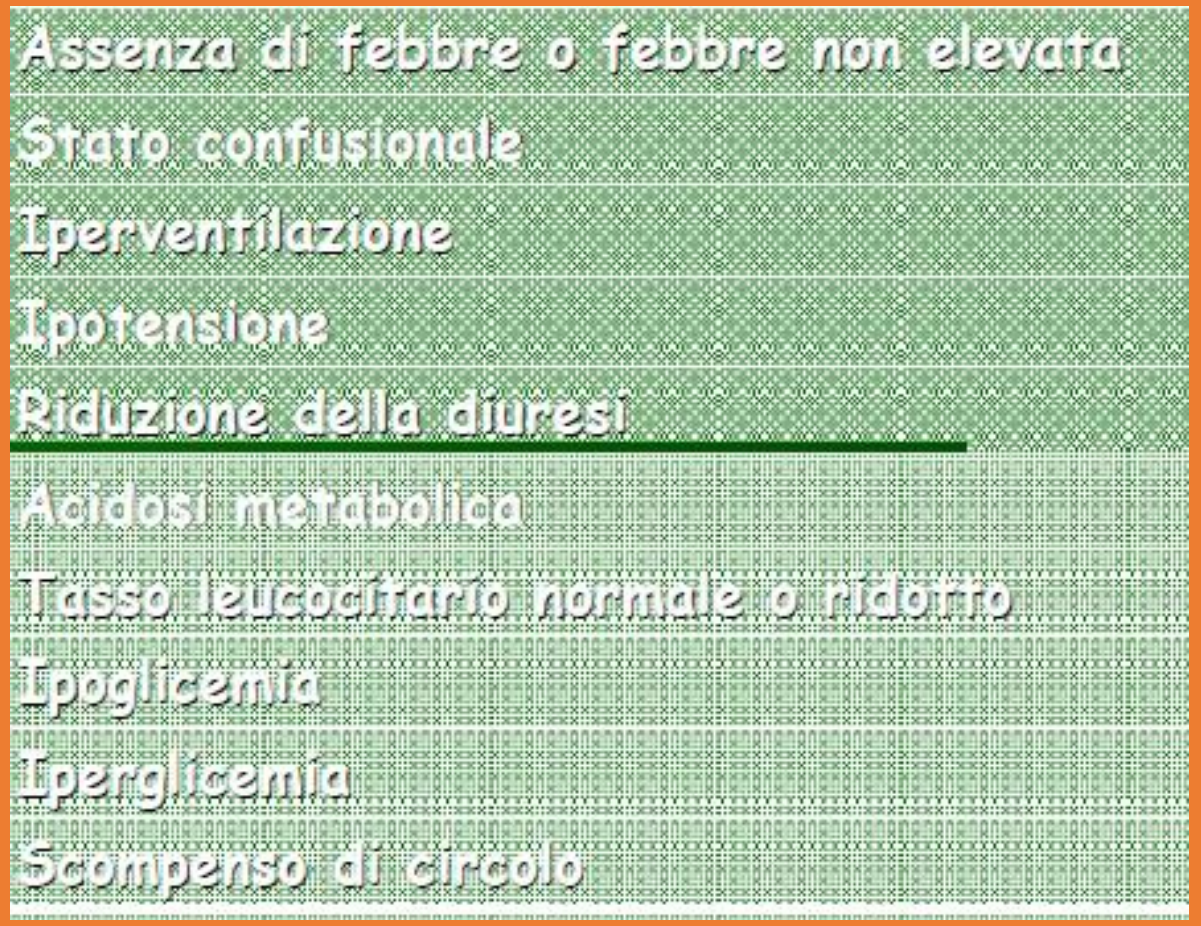
…e una teoria di cui ricorre il 58° anniversario

- **L’età di per sé rappresenta un fattore di rischio per lo sviluppo di infezioni in quanto associata a modificazioni della risposta immunitaria, alterazioni fisiologiche quali ridotto riflesso della tosse, minore perfusione tissutale e rallentati processi di riparazione delle ferite.**
- **Altre condizioni favorenti: ridotta attività fisica e/o degenza letto, scadute condizioni igieniche istituzionalizzazione, malnutrizione, patologie debilitanti come diabete mellito, BPCO, enfisema polmonare, demenza, disturbi circolatori, scompenso cardiocircolatorio, terapia anti-neoplastica**

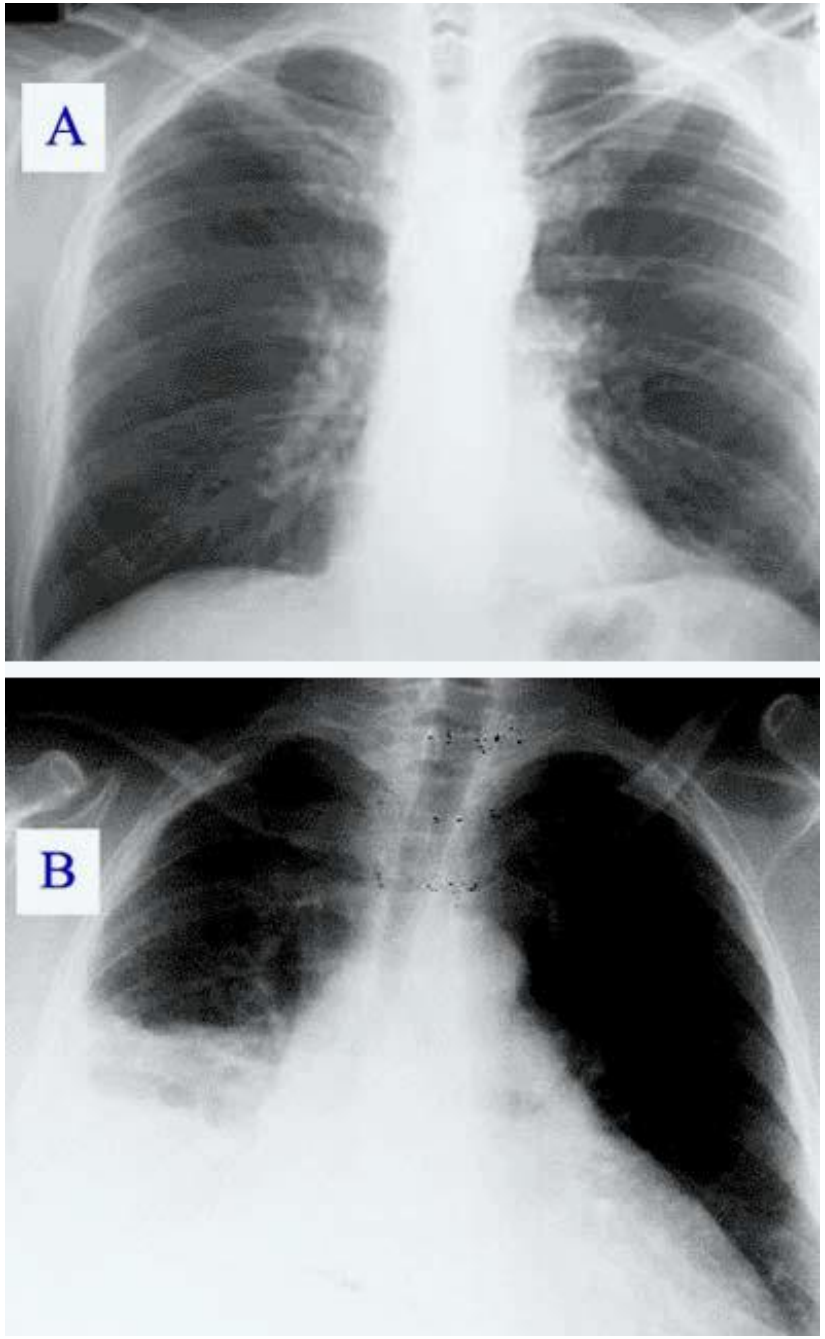
Infezioni più frequenti nell'età >65 anni



Atipie nelle manifestazioni infettive in >65 anni



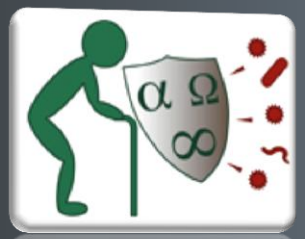
- In developed countries, the major threat to elderly individuals comes from respiratory infections caused by a combination of classic bacteria (e.g. pneumococci) and respiratory viruses (e.g. influenza virus). Among respiratory infections, influenza is the most serious threat to persons over 65 years of age and, according to the World Health Organization (WHO), is responsible for the most deaths; the death rate for pneumonia is eight times higher in the elderly compared to younger adults. Urinary tract infections, often aided by indwelling urinary catheters, are caused by *Escherichia coli* (mainly in women), *Klebsiella spp*. (especially *K. pneumoniae)*, *Proteus spp.* and *Morganella morganii* (mainly in men) and are the second most common type of infection



- Following close behind are infective endocarditis (caused by *Staphylococcus aureus* strains, which are often methicillin-resistant, as well as *Streptococcus bovis* and Enterococci) and septicemia, manifested through numerous bacteria in the blood.
- Infection with “unusual” pathogens such as *Cryptococcus spp*., *Mycobacterium tuberculosis* and *Listeria spp.* is comparatively rare but nevertheless increased in the elderly and is often overlooked.
- Because of higher rates of hospitalization, older individuals are more susceptible to nosocomial infections, including those caused by antibiotic-resistant organisms

- In less developed countries, malaria, hepatitis A and B and HIV are some of the most relevant infections with increased severity in older populations.
- *Plasmodium* has a more severe clinical manifestation in the elderly; older patients have a greater parasite density, require a longer hospital stay and develop more complications, resulting in a significantly higher rate of mortality
- WHO reports that more than half of the documented deaths from hepatitis A occur in elderly persons in developing countries. Acute hepatitis B infection, which is rarely fatal in younger populations, can cause mortality as high as 10–15% in elderly populations

INVECCHIAMENTO E IMMUNOSENESCENZA

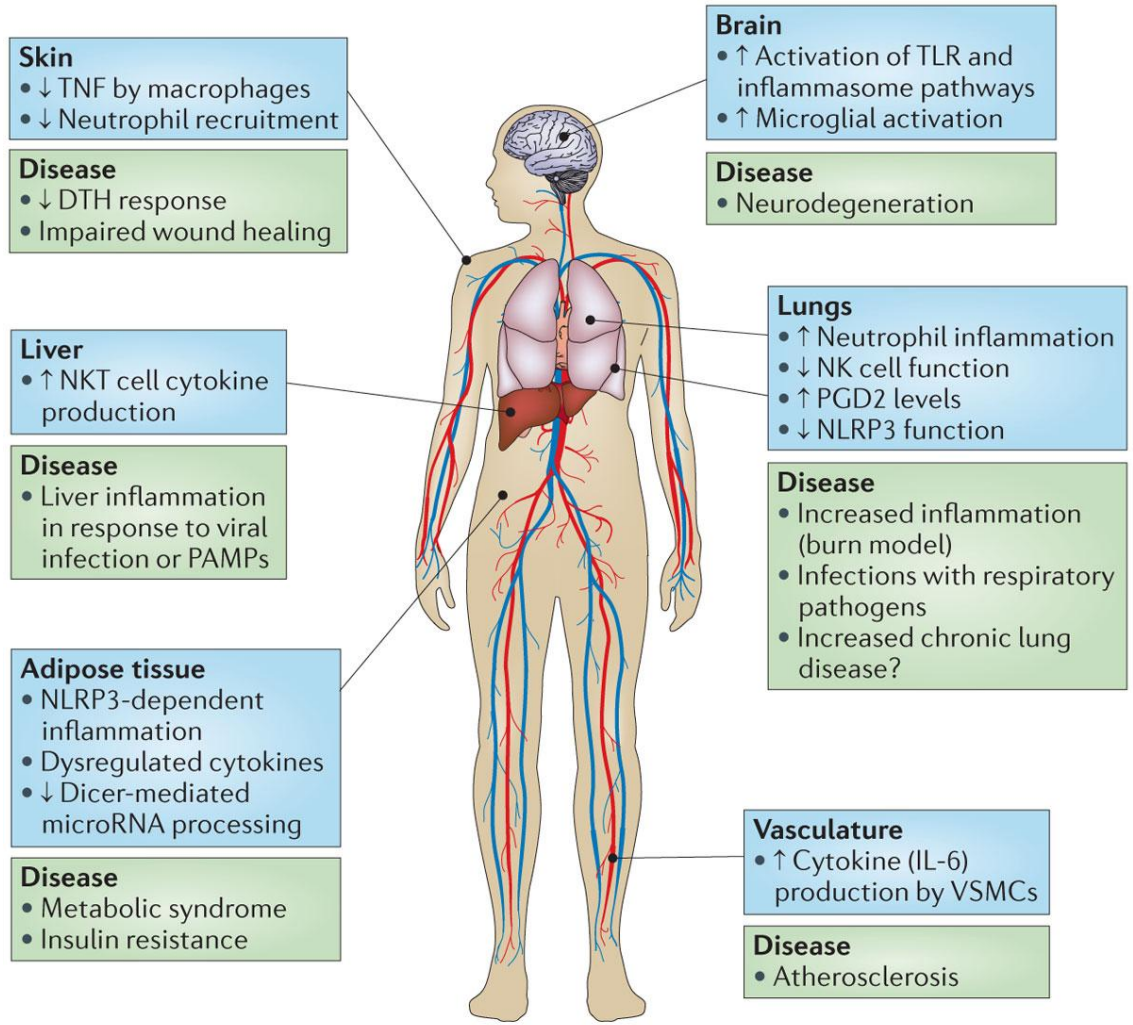


Studio dei soggetti centenari

“Teoria del rimodellamento”

Immunosenescenza

Fenomeno dinamico
e non uniforme



Nature Reviews | Immunology

Evidence for Decline in Immune Function with Aging

Aged Individuals have:

1) Increased incidence of INFECTIONS:
   For example: pneumonia, influenza, tuberculosis, meningitis, urinary tract infections

2) Increased incidence of AUTOIMMUNITY:
   For example: rheumatoid arthritis, thyroiditis (Graves-hyper/Hashimoto-hypo), autoantibodies

(Also related to HLA genes)

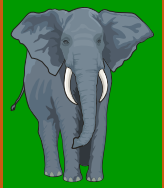
Evidence for Decline in Immune Function with Aging

Aged Individuals have:

3) Increased CANCER :
For Example: prostate, breast, lung, throat/neck/head, stomach/colon/bladder, skin, leukemia, pancreatic

4) Better TOLERANCE to organ transplants:
Kidneys, skin, bone marrow, heart (valves), liver, pancreas, lungs

Successful aged per età

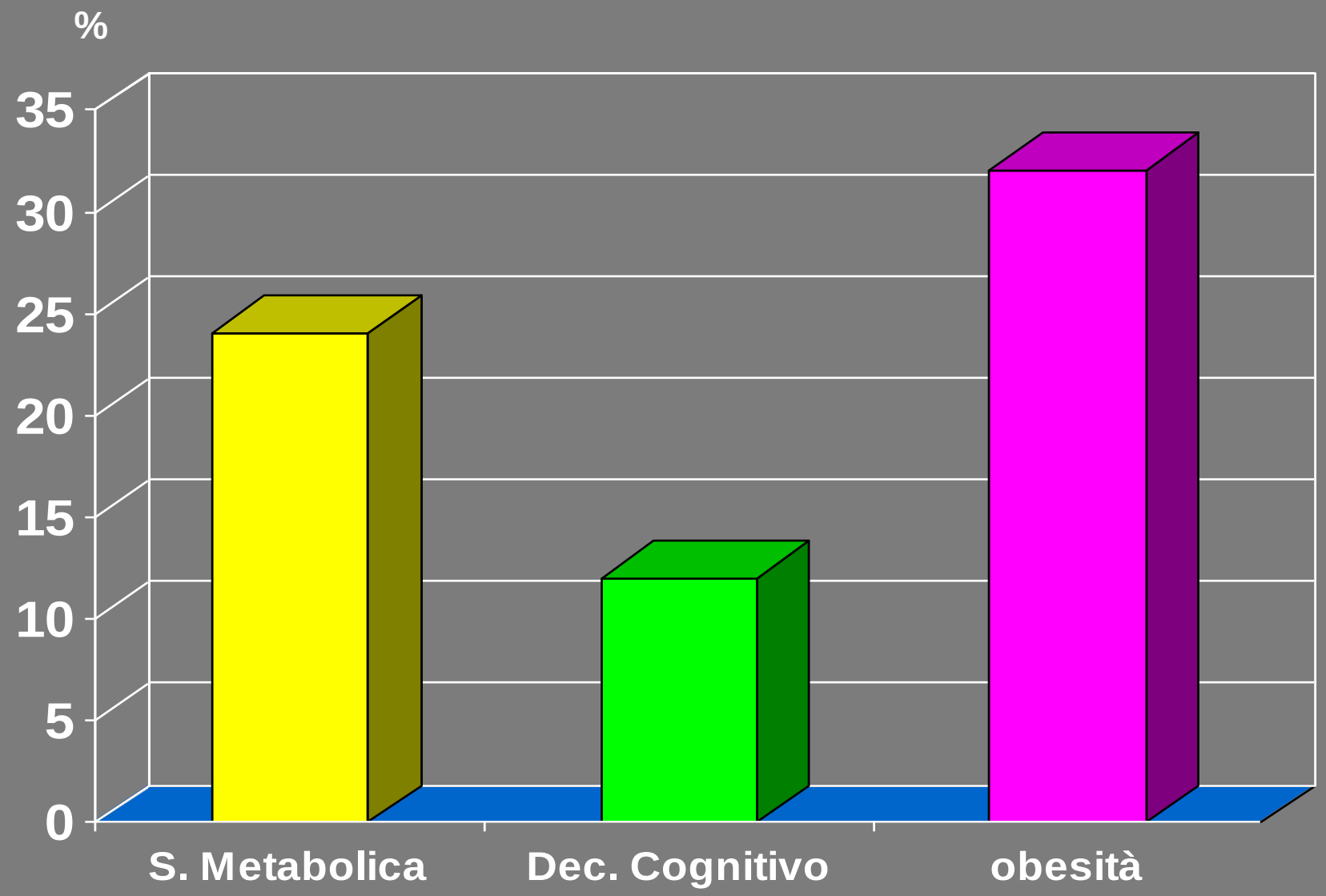


Successful Aging Chieti Study 2006

	Arruolati			
	Totali		Successful	
	n°	%	n	%
65-74	210	64.4	88	41.9
75-84	90	46.4	49	54.5
>85	20	25.0	11	55.0
	321		148	

Prevalenza

Successful Aging Chieti Study 2006



Cellule staminali ematopoietiche

- Riduzione della capacità di auto-rigenerazione con l'età
- ↓ propensione alla linfopoiesi
- ↓ abilità delle cellule stromali di supportare la linfopoiesi

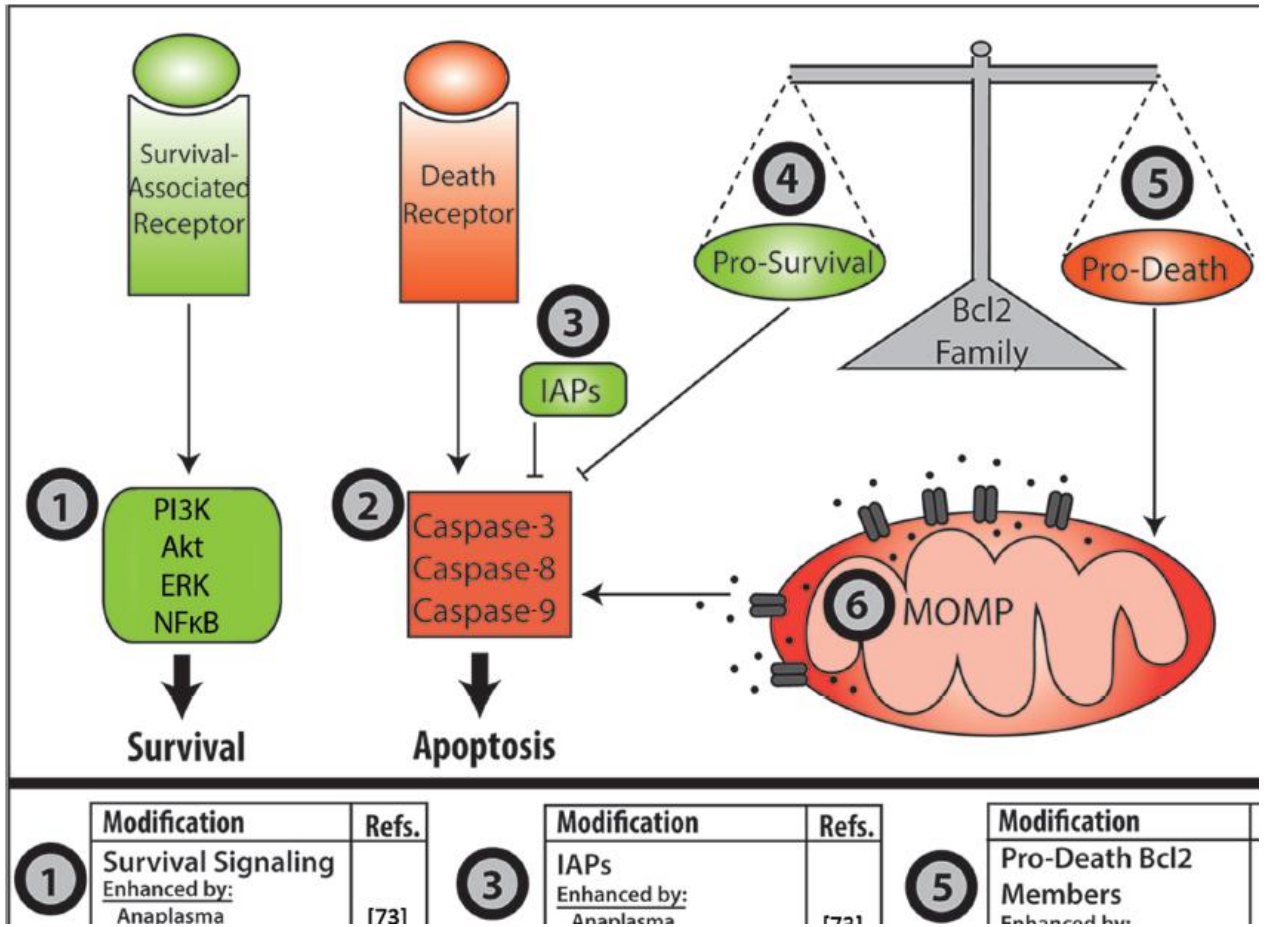
Sistema immunitario innato

- **Difesa di prima linea, aspecifica, immediata**
- **Componenti principali: PMN, cellule dendritiche, macrofagi, cellule NK, complemento**
- **Alcune funzioni dell' immunità innata sono conservate negli anziani sani (p.es. fagocitosi), mentre altre sono diminuite (p.es citotossicità NK per cellula)**

In aging PMNs, expression of pro-survival factors wanes and pro-death factors accumulates, and this imbalance is critical

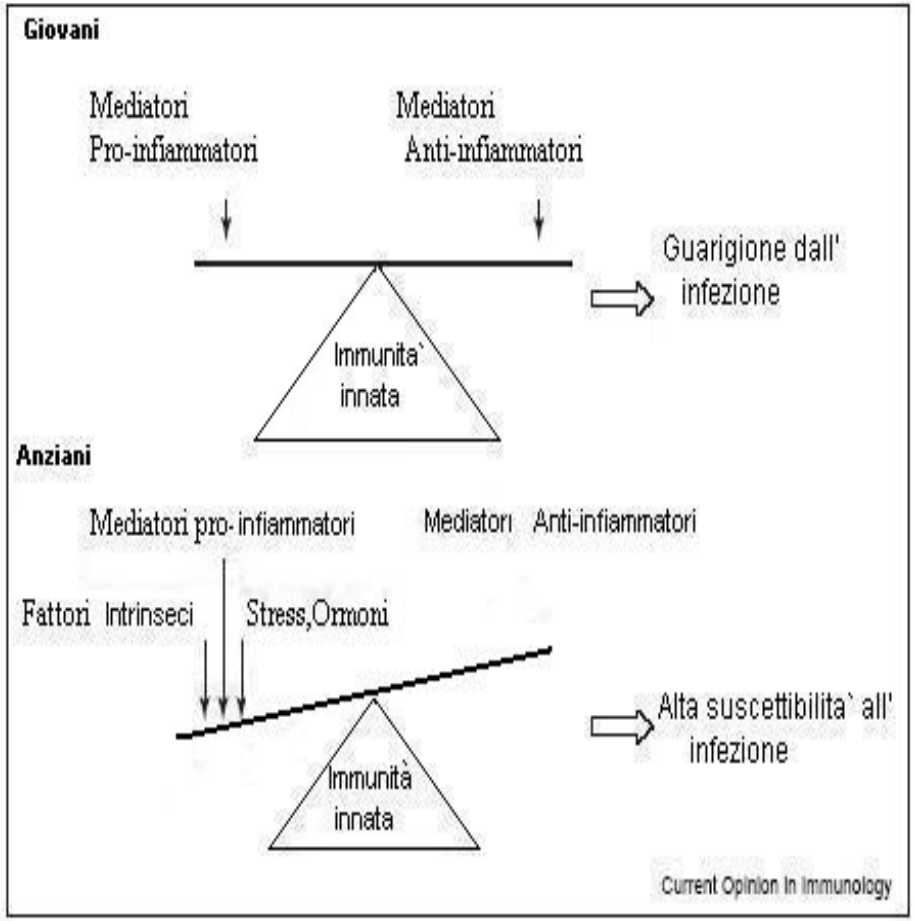
Regulation of Human Neutrophil Apoptosis and Lifespan in Health and Disease

Jenna M. McCracken[1,2] and Lee-Ann H. Allen[1–4]



Citochine e invecchiamento

- **Lo stress antigenico cronico stimola il sistema immunitario con secrezione di citochine proinfiammatorie (IL2,TNFα)**
- **Inflamm-aging: stato cronico infiammatorio a basso livello tipico dell'età anziana**
- **Causa la predisposizione all' insorgenza di patologie su base infiammatoria (p.es. aterosclerosi, diabete tipo 2, sarcopenia, m. di Alzheimer)**



Some Aging Related Effects on B-Cells

- Decreased number of circulating and peripheral blood B cells
- Alteration in B-cell repertoire (diversity)
- Decreased generation of primary and secondary memory B cells
- General decline in lymphoproliferative capacity

Some Aging-Related Effects on T-cells

- General decline in cell mediated immunological function
- T-cell population is hyporesponsive
- Decrease responsiveness in T-cell repertoire (i.e. diversity of CD8+ T-cells)
- Decline in new T-cell production
- Increase in proportion of memory and activated T-cells while naïve T-cells decrease
- Diminished functional capacity of naïve T-cells (decreased proliferation, survival, and IL-2 production)
- Senescent T-cells accumulate due to defects in apoptosis
- Increased proportion of thymocytes with immature phenotype
- Shift in lymphocyte population from T-cells to NK/T cells (cell expressing both T-cell receptor and NK cell receptors)

Influence of Aging on Macrophages and Granulocytes

General functional impairment of macrophages and granulocytes

GM-CSF is unable to activate granulocytes from elderly subjects (e.g.: superoxide production and cytotoxic abilities)

Polymorphonuclear neutrophils appear to possess higher levels of surface markers CD15 and CD11b and lesser vesicles containing CD69 which lead to the impairment observed to destroy a bacteria

In elderly subjects the monocyte phenotype shifts (i.e. expansion of CD14dim and CD16 bright subpopulations which have features in common with mature tissue macrophages)

Macrophages of aged mice may produce less IFN-γ, less nitric oxide synthetase, and hydrogen peroxide.

Aging-Related Changes in Natural Killer (NK) Cells

General decline in cell function

Good correlation between mortality risk and NK cell number

Increased in proportion of cells with high NK activity (i.e. CD16+, CD57-)

Progressive increase in percentage of NK cells

Impairment of cytotoxic capacity per NK cell

Increase in NK cells having surface molecule CD56 dim subset

Alterazioni nel compartimento linfocitario T con l'età

- ↓ cellule CD45RA+ (naive)
- ↑ cellule CD45RA- (memoria)
- ↓ apoptosi CD8+
- ↑ apoptosi CD4+
- ↑ cellule CD28-
- ↓ lunghezza dei telomeri
- ↑ danno del DNA

PRINCIPALI CARATTERISTICHE DELL'IMMUNOSENESCENZA

Franceschi et al. Italian Journal of Medicine, 2011

✓ ***Involuzione del timo***

✓ ***Remodelling linfocitario***

max immunità cellulo-mediata
max cellule T
max CD8+ (CD4/CD8 <1)

- Diminuzione dei linfociti T naïve e aumento delle cellule di memoria
- Aumento delle cellule T attivate CD28–
- Aumento delle cellule responsive ad antigeni del *Cytomegalovirus*
- Diminuzione dell'attività di output del timo
- Diminuzione del numero di linfociti T_{REC+} in periferia
- Elevato numero di espansioni monoclonali e oligoclonali dei sistemi B e T
- Riduzione del repertorio dei linfociti B e T
- Aumentata risposta di tipo TH_2
- Aumento della produzione di citochine proinfiammatorie (in particolare IL-1, IL-6 e TNF-alfa)
- Diminuzione della funzionalità dei neutrofili e dei monociti
- Aumento del numero di cellule natural killer
- Diminuzione della funzionalità delle cellule dendritiche

✓ ***Alterazione del pattern di produzione delle citochine***

"inflammaging" e "anti-inflammaging"

Determinazione del Fenotipo di Rischio Immunologico (IRP)

Studi longitudinali effettuati su coorti di 80- e 90enni (studi OCTO e NONA) hanno messo in rapporto un "cluster" di parametri immunologici con la mortalità a distanza di 2, 4 e 6 anni nei diversi follow-up

- CD4:CD8<1
- ↓ risposta delle cellule T ai mitogeni
- ↑ linfociti T CD8+ CD28-
- ↓ numero linfociti B
- sieropositività per il Cytomegalovirus (CMV)

La presenza di questi parametri è predittiva di diminuzione di sopravvivenza

PROFILO DI RISCHIO IMMUNOLOGICO (IRP)

Vasto et al. Immun and Ageing, 2007

Mortalità e morbilità

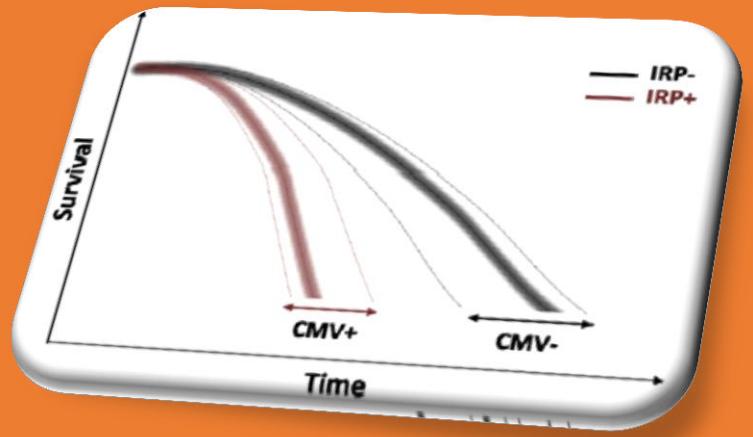
Rapporto CD4/CD8 < 1
Bassa risposta linfoproliferativa a mitogeni
Aumento dei lifociti T CD8+CD28- e CD8+CD57+
Basso numero di linfociti B
Sieropositività per il CMV
Espansione clonale delle cellule CD8+ con recettori per il CMV
Elevata percentuale di cellule disfunzionali tra le CD8+ CMV-specifiche

Studi OCTO e NONA

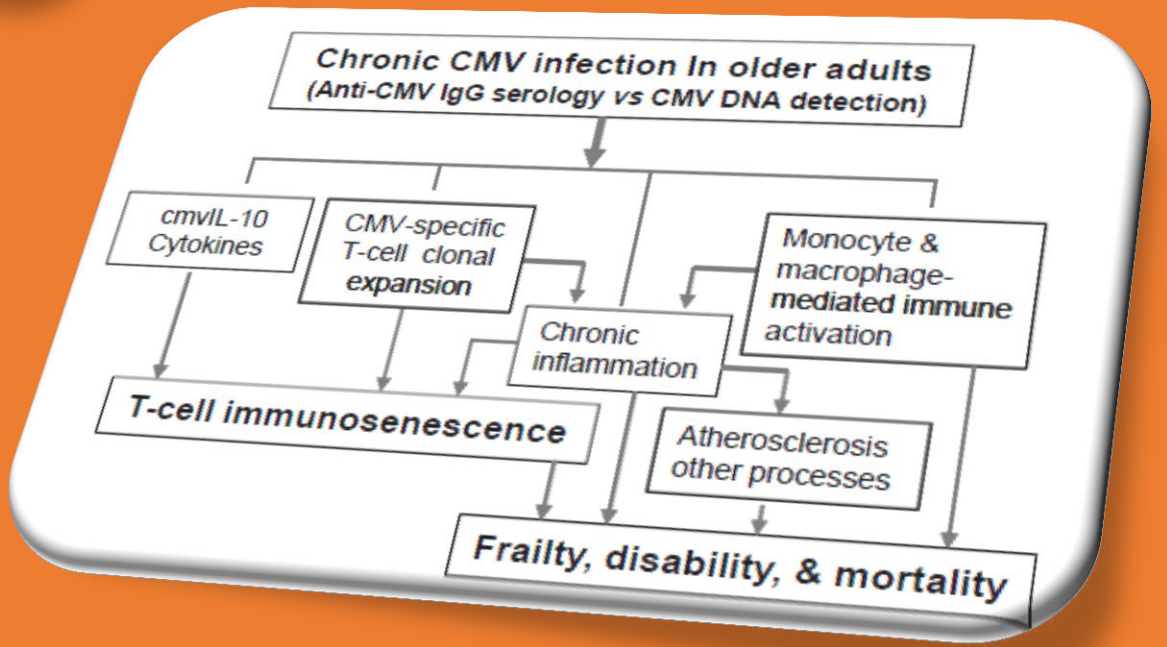
IRP predittivo di ridotta sopravvivenza a 2, 4 e 6 anni

RUOLO DEL CITOMEGALOVIRUS (CMV)

Derhovanessian et al. Curr Opin Immunol, 2009



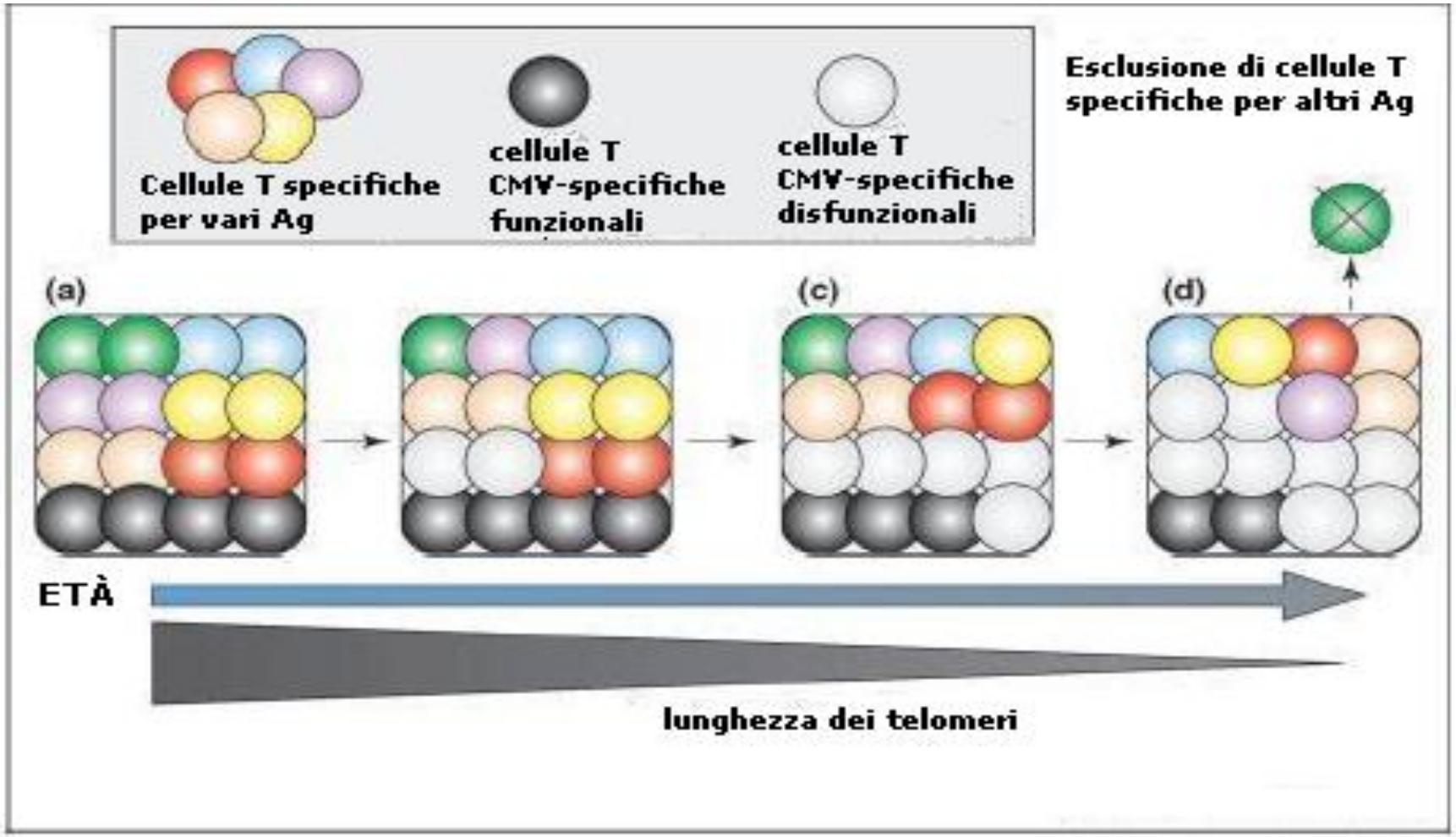
Leng et al. J Am Geriatr Soc, 2011



CMV

- **nel sangue degli anziani troviamo:**
  - **>25% di T CD8+ CD28- specifici per un antigene strutturale del CMV, fosfoproteina 65 (pp65), disfunzionali (anergici)**
  - **↓ IFN-γ in seguito a stimolazione specifica con pp65**
  - **↑ resistenza all' apoptosi**

Effetti dell' accumulo di linfociti T CMV-specifici



frontiers in
IMMUNOLOGY

REVIEW ARTICLE
published: 13 September 2013
doi: 10.3389/fimmu.2013.00271

Human T cell aging and the impact of persistent viral infections

T. Fülöp[1], A. Larbi[2] and G. Pawelec[3]*

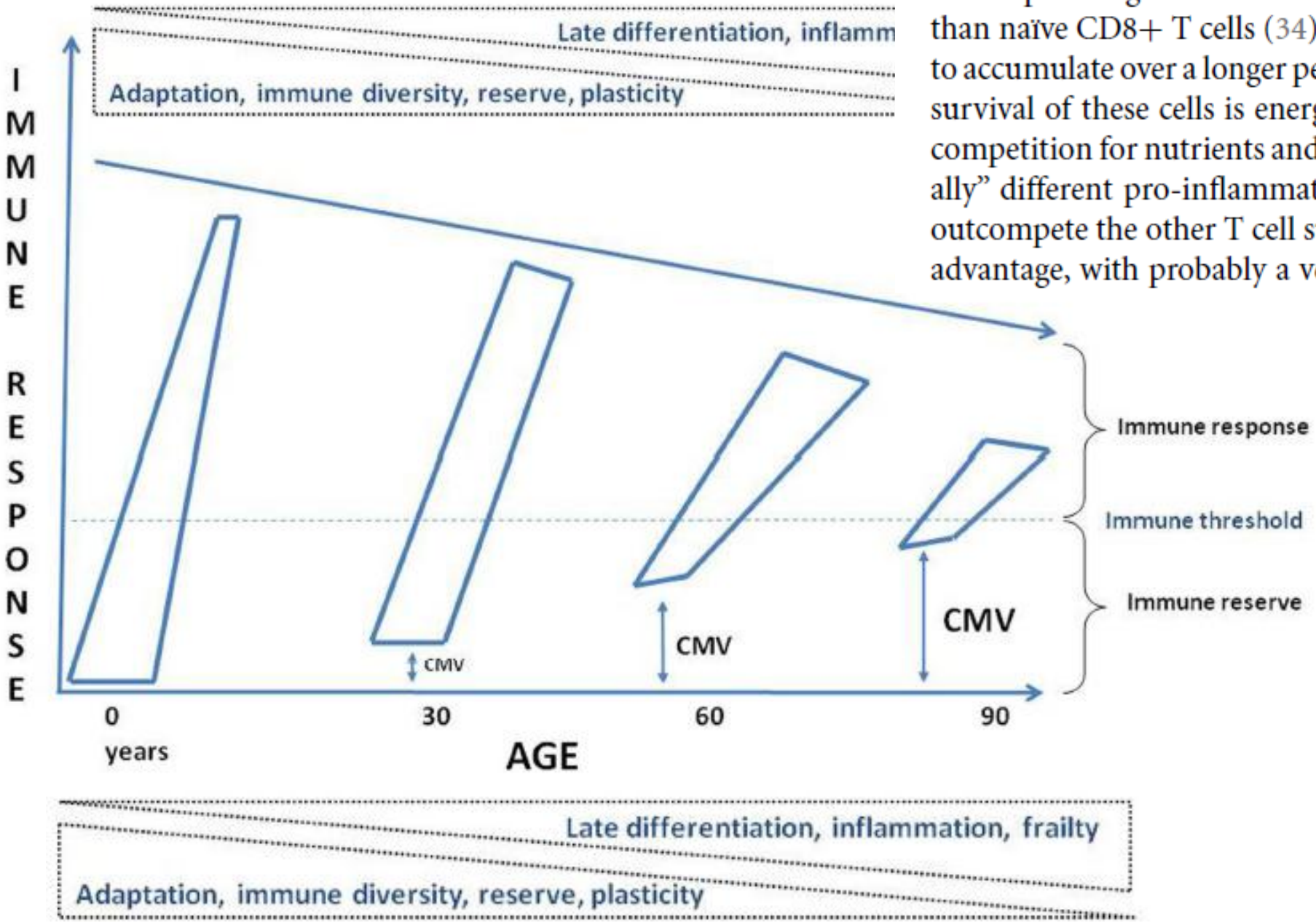
The aging of the immune system is a dynamic process which may at least partly reflect adaptation of the response to the evolving pathogen milieu (7, 8). Not all compartments of the immune response are aging in the same way, at the same speed or the same direction (9, 10). There was an assumption that all parts and functions of the immune system were decreasing with age, but currently the realization that compensatory increases may be developing over time is gaining ground. Even previously identi-

The price paid by the adaptive immune system to maintain CMV in a latent phase is very high in terms of resource dedication (70, 71). In elderly subjects as many as 50% of CD8+ and 30% of CD4+ T cells can be CMV-specific (72) at the expense of

	CMV	HIV	HBV	EBV	VZV	HSV-1
Expansion (Tetramer)	+++	+	+	+	–	–
Viral Load	+/ –	+	+/ –	+/ –	+/ –	+/ –
Reactivation	?	++	?	?	+/ –	+/ –
Phenotype of Specificity	TEMRA	EM TEMRA	EM	EM	CM EM	EM
Immunological Aging	+++	++++	+	++	–	–
Clinical Impact Young	Moderate	Severe	Mild	Moderate	Mild	Mild
Clinical Impact Elderly	Moderate	Severe	Mild	Moderate	Severe	Mild

FIGURE 2 | Impact of different chronic viral infections on the immune system and clinical consequences in young and elderly subjects. The immunological and clinical impact of these viral infections is different in young and elderly and even among elderly; however they present a persistent antigenic stimulation throughout life.

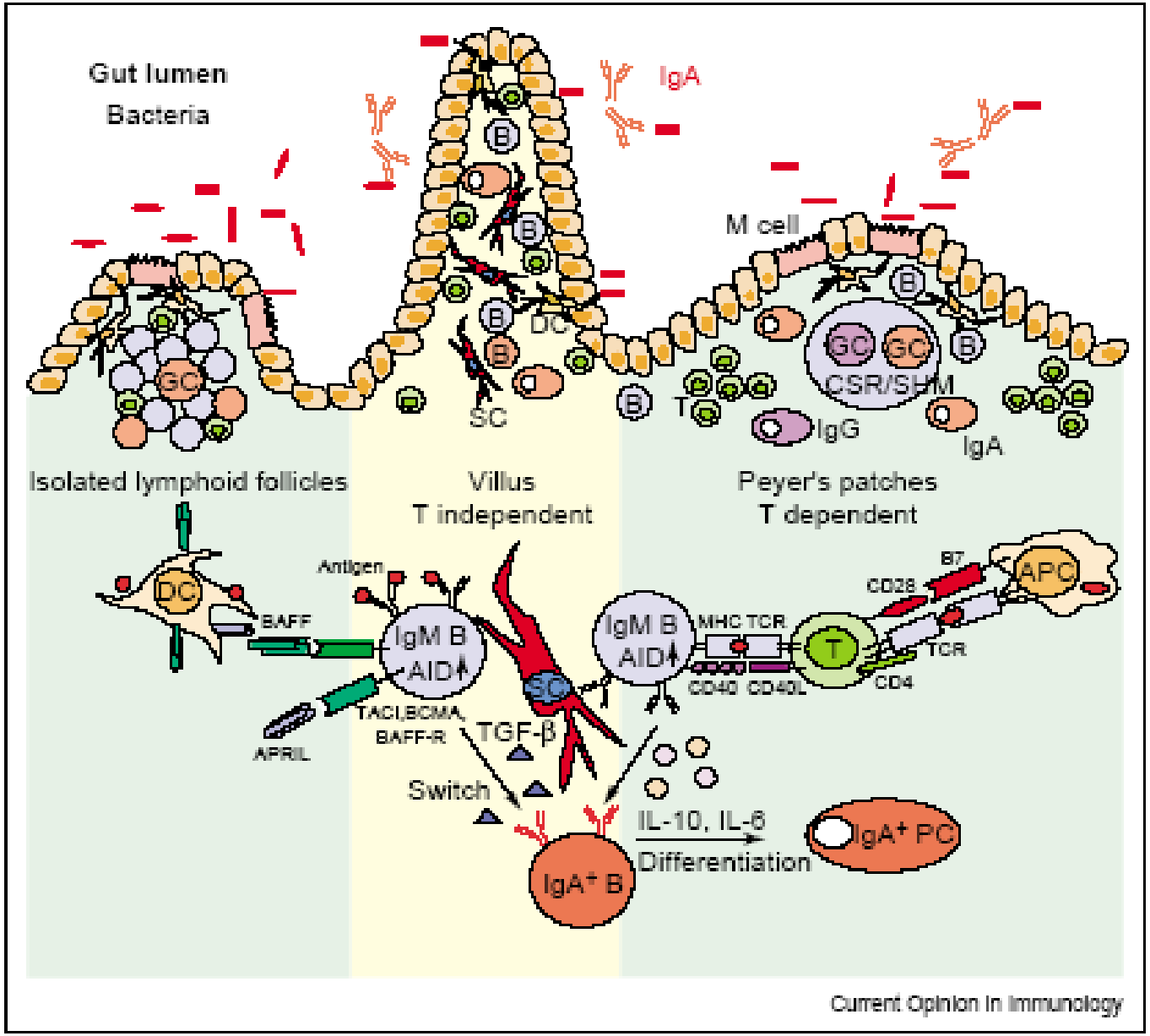
replicatively senescent (12, 84, 85). Furthermore, these TEMRA cells express high levels of Bcl-2 and are more apoptosis-resistant than naïve CD8+ T cells (34). This means that they will continue to accumulate over a longer period of time (i.e., during aging). The survival of these cells is energy-consuming. It is clear that in the competition for nutrients and factors to maintain these "functionally" different pro-inflammatory CD8+ T cells, they will largely outcompete the other T cell subpopulations. They have a survival advantage, with probably a very strong metabolic advantage too.



You Are What You Host: Microbiome Modulation of the Aging Process

As you look in the mirror, you may only see yourself staring back, but in reality, you are not alone; you share your body with trillions of others. Contained on and within our bodies thrives a dynamic population of microbes that form a "metaorganism" comprising ten bacterial cells for every one of our own. Despite coevolving in the presence of this "microbiome" for 500 million years (Cho and Blaser, 2012), only recently have advances in sequencing technology allowed us to appreciate the complexities of this relationship and the manner by which genomes within metaorganisms interact and affect one another. Interindividual variations in the microbiome impact multiple human pathologies, from metabolic syndrome to cancer (Cho and Blaser, 2012). However, new data in invertebrate systems indicate that microbes extend their effects beyond host pathology to systemic modulation of the rate of aging.

commensal bacteria, defining the metagenome—the ensemble of host and microbiota DNA—and by extension, the metatranscriptome, proteome, and metabolome. With endeavors such as the Human Microbiome Project just beginning (Cho and Blaser, 2012), research into the complexity of mammalian microbiome dynamics is in its infancy. Assigning causality to effects


Gut lumen
Bacteria
IgA
M cell
B
DC
GC
GC
GC
CSR/SHM
SC
T
IgG
IgA
Isolated lymphoid follicles
Villus
T independent
Peyer's patches
T dependent
Antigen
DC
BAFF
IgM B
AID
SC
IgM B
AID
MHC TCR
T
B7
CD28
APC
TCR
CD4
CD40
CD40L
TACI,BCMA,
BAFF-R
APRIL
TGF-β
Switch
IL-10, IL-6
Differentiation
IgA+ PC
IgA+ B
Current Opinion in Immunology

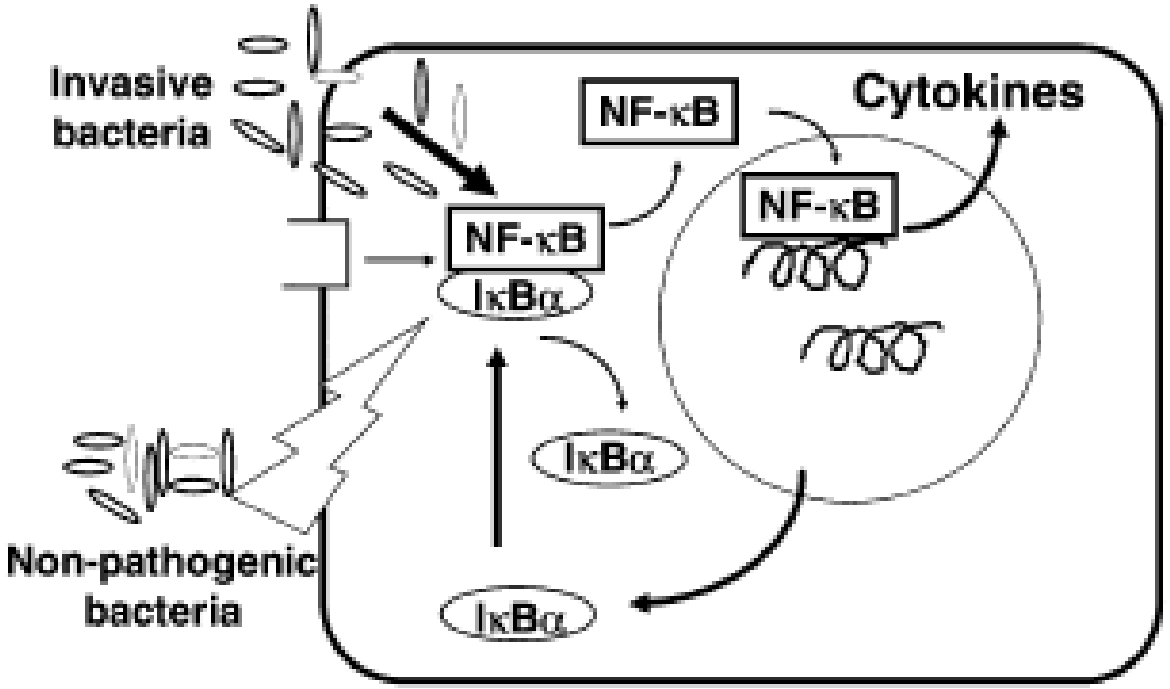


Fig. 1. Schematic illustration of the mechanism by which some non-pathogenic organisms, commensals or even probiotics may antagonise the inflammatory effects of invasive pathogens. The transcription factor, NF-kB is a central regulator of proinflammatory cytokine production triggered by invasive pathogens such as salmonella organisms. Some non-pathogens appear to offset these effects by delaying the degradation of the counter-regulatory transcription factor IkB. Based on data by Neish et al. [58].

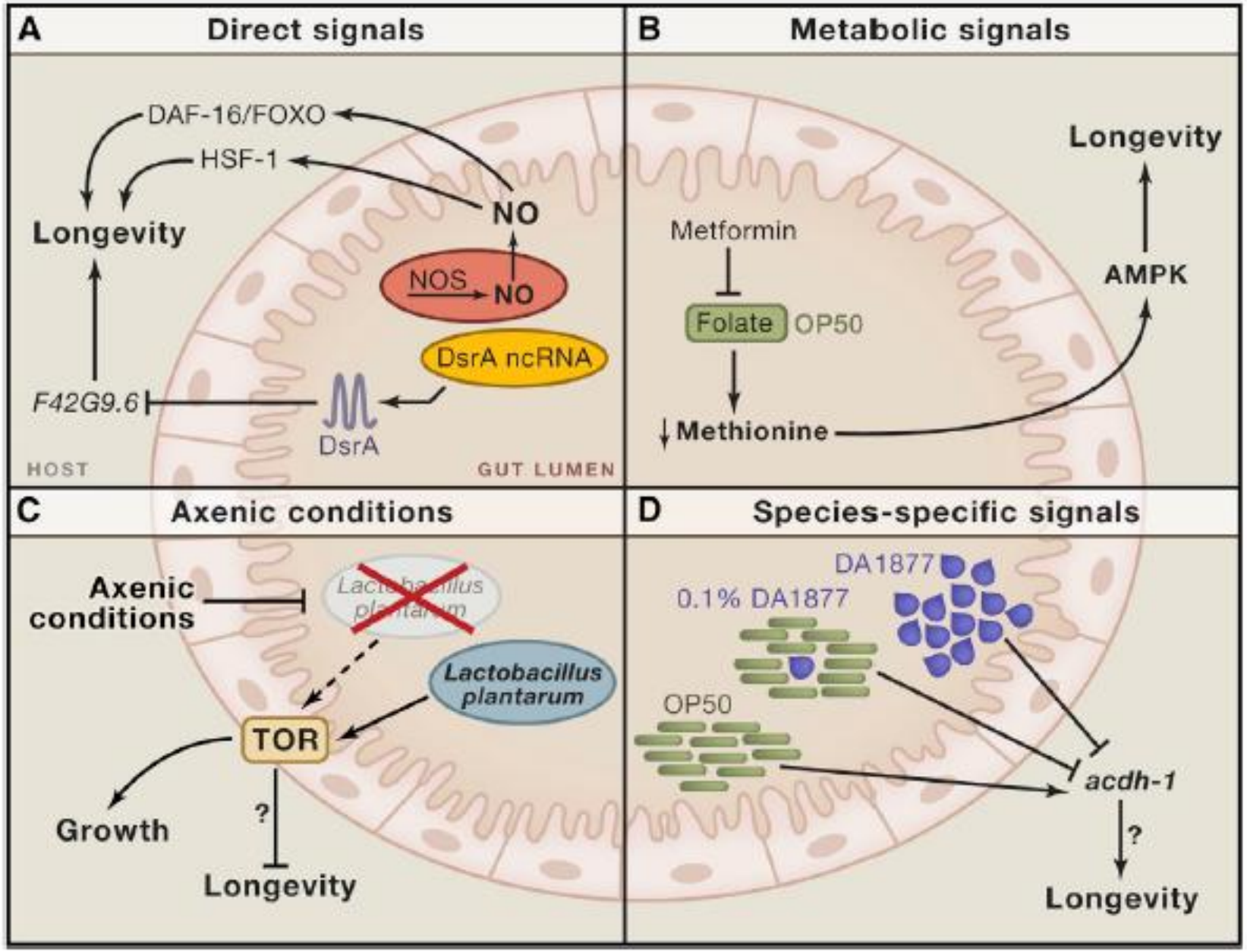


Figure 1. Microbe Modulation of Invertebrate Aging and Physiology

(A) Bacterial-derived signals NO and ncRNAs regulate *C. elegans* longevity.

(B) Metformin increases *C. elegans* lifespan via effects on bacterial folate metabolism.

(C) *L. plantarum* drive *Drosophila* growth under low-nutrient conditions via the longevity modulator TOR.

(D) Different bacterial species elicit specific transcriptional responses in *C. elegans*.

REVIEW Open Access

Immunosenescence in vertebrates and invertebrates

Ludmila Müller[1*], Tamas Fülöp[2] and Graham Pawelec[3]

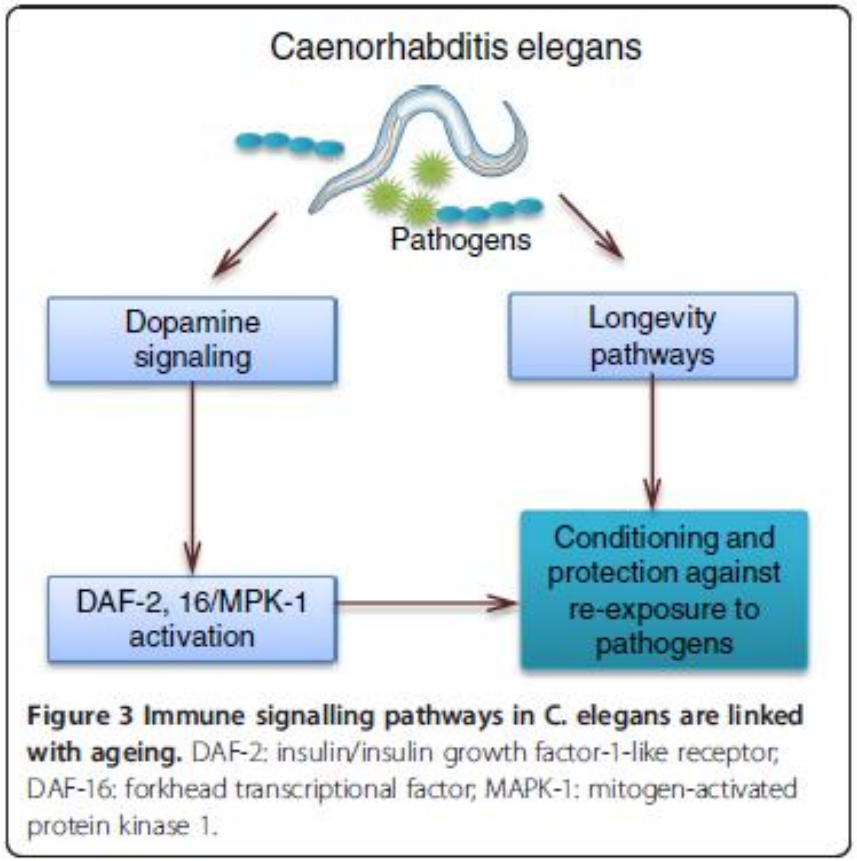
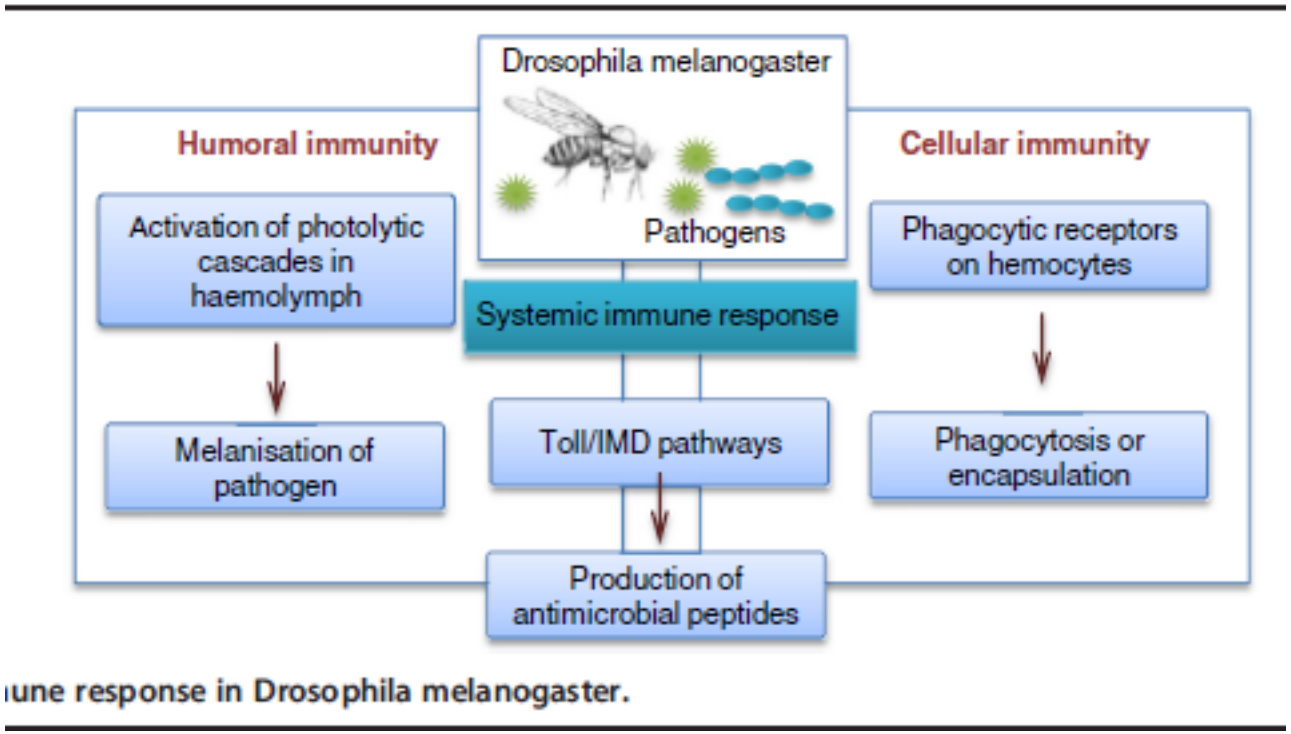


Figure 3 Immune signalling pathways in C. elegans are linked with ageing. DAF-2: insulin/insulin growth factor-1-like receptor; DAF-16: forkhead transcriptional factor; MAPK-1: mitogen-activated protein kinase 1.



…une response in Drosophila melanogaster.

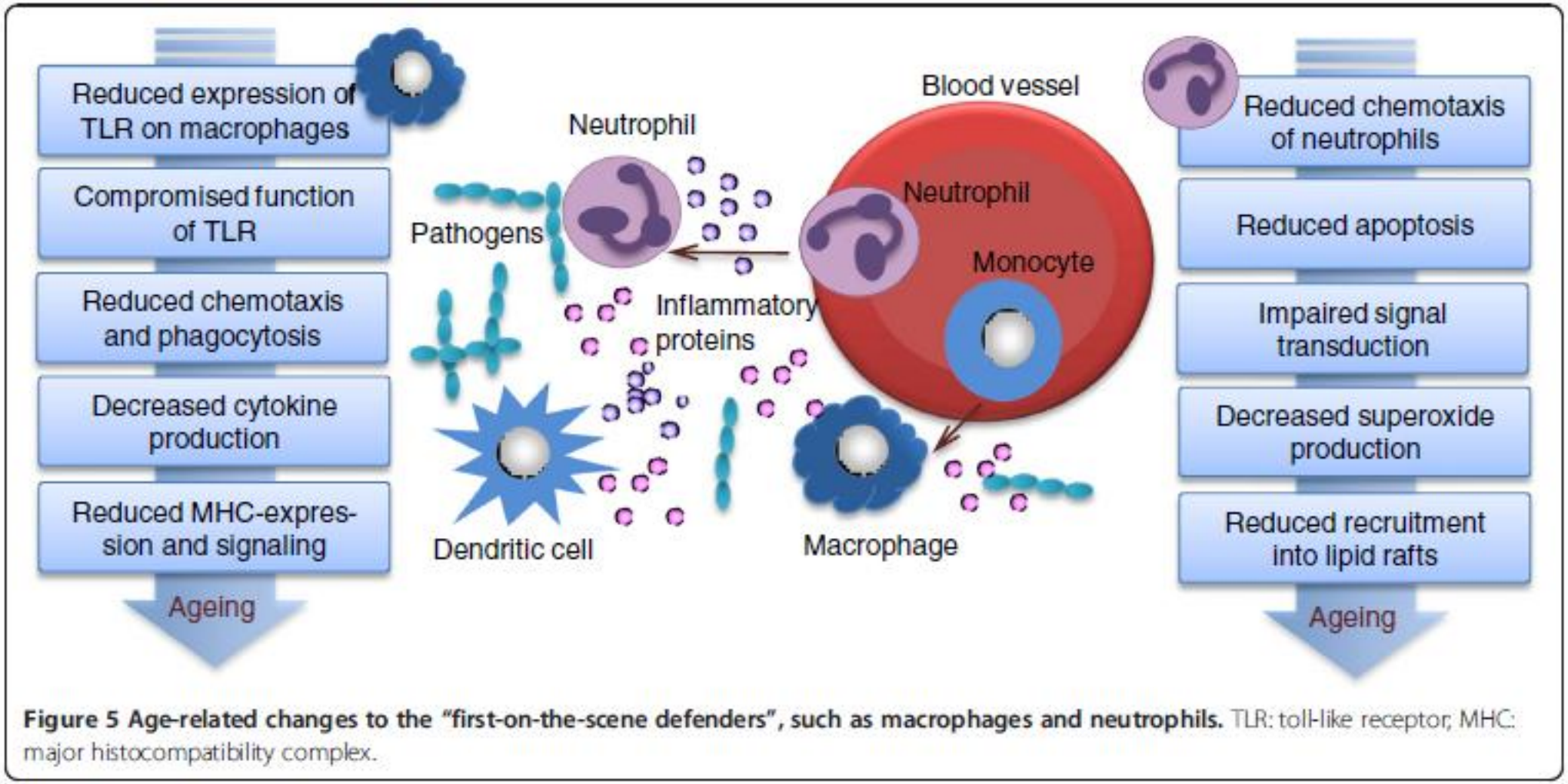


Figure 5 Age-related changes to the "first-on-the-scene defenders", such as macrophages and neutrophils. TLR: toll-like receptor; MHC: major histocompatibility complex.

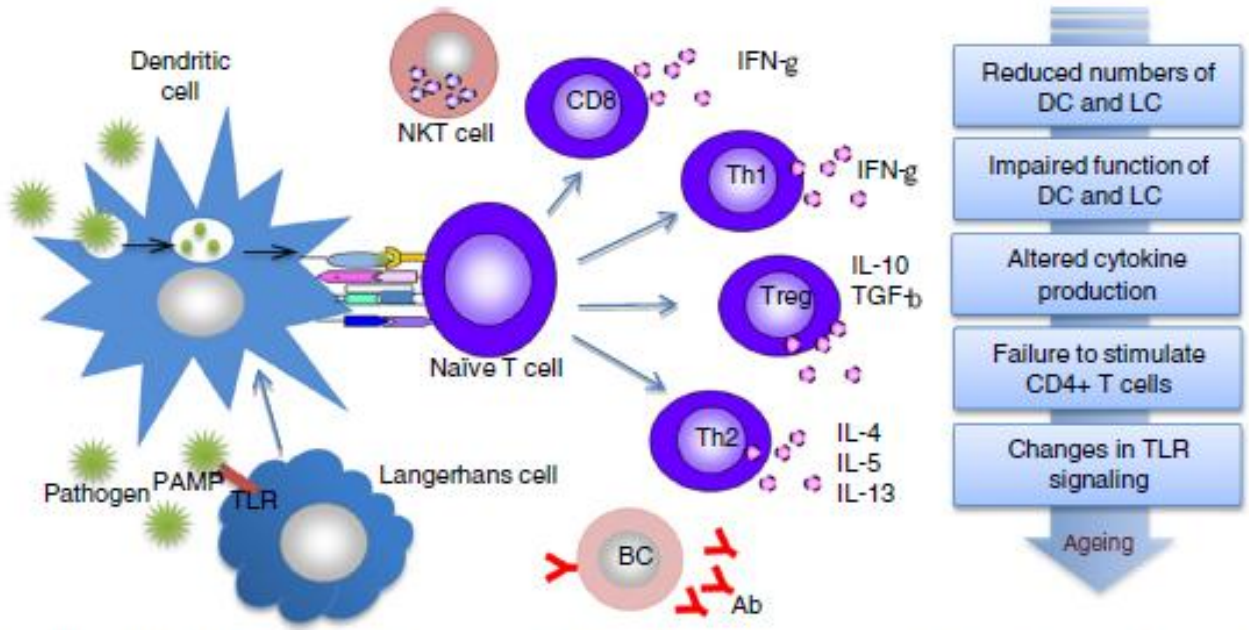


Figure 7 Role of dendritic cells and Langerhans cells in immunity and their age-associated changes. NKT cells: natural killer T cells; TLR: toll-like receptor; PAMP: pathogen-associated molecular pattern; BC: B cell; Ab: antibody; CD8: CD8-positive T cell; Th1: T helper 1 cell; Treg: regulatory T cell; Th2: T helper 2 cell; IFN-γ: interferon gamma; IL-10: interleukin 10; TGF-β: transforming growth factor beta; IL-4: interleukin 4; IL-5: interleukin 5; IL-13: interleukin 13.

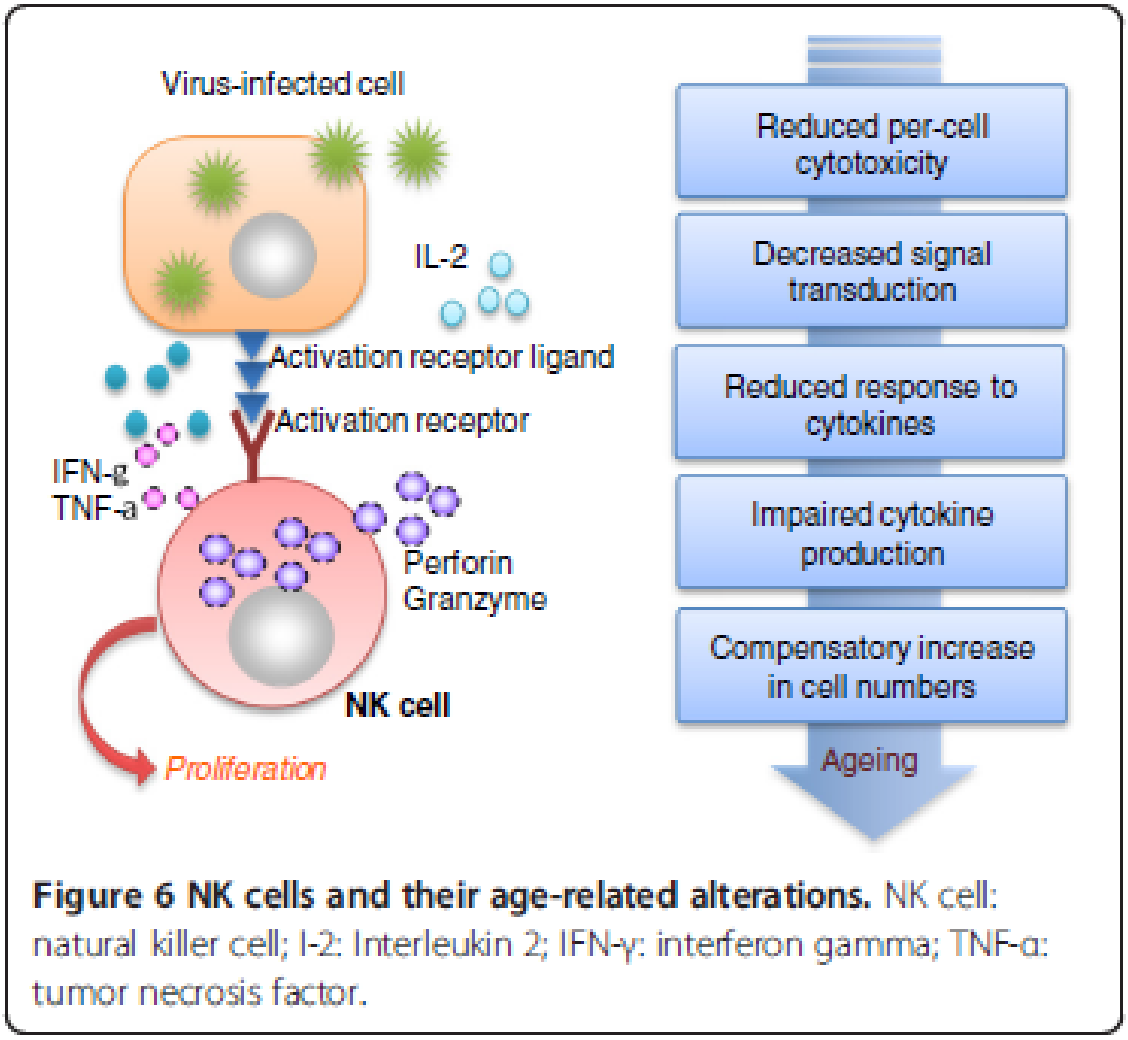


Figure 6 NK cells and their age-related alterations. NK cell: natural killer cell; I-2: Interleukin 2; IFN-γ: interferon gamma; TNF-α: tumor necrosis factor.

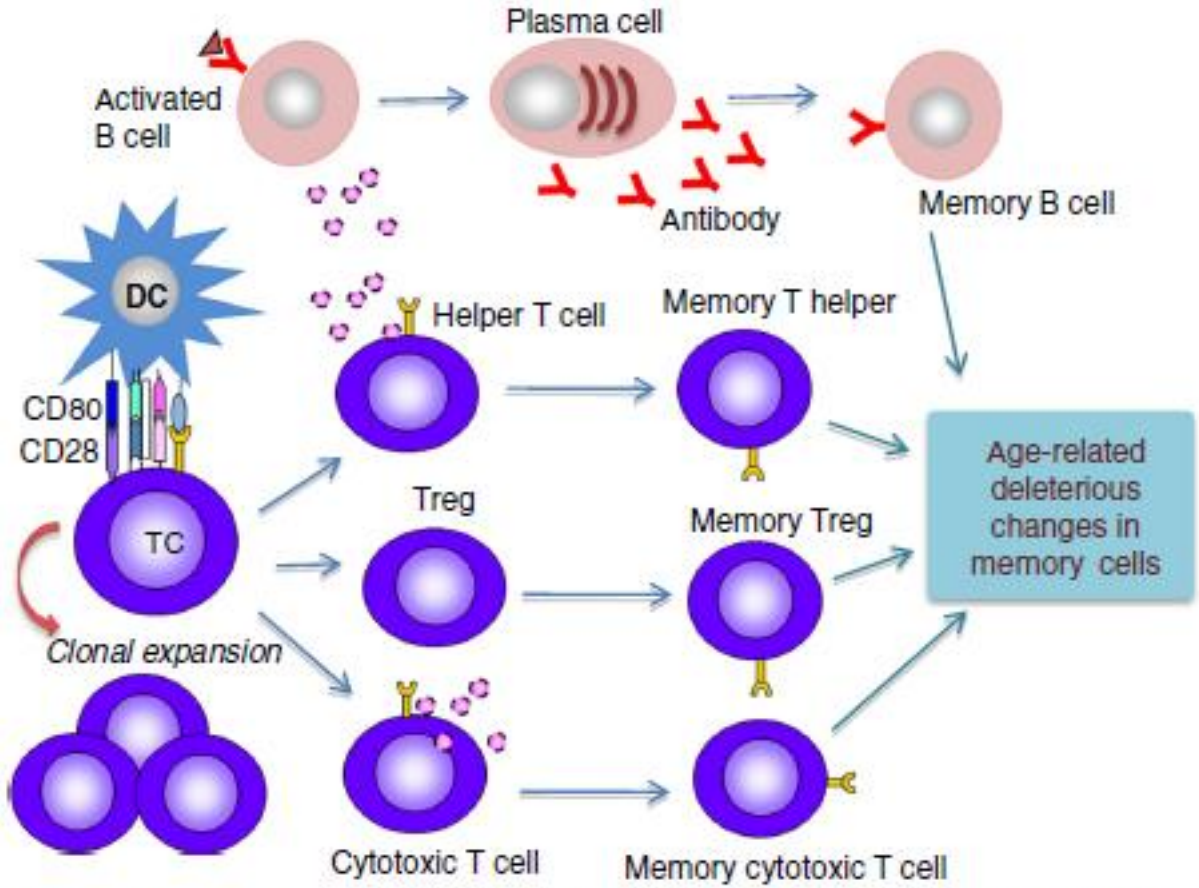


Figure 8 Interaction of T cell and dendritic cell leading to T-cell activation, clonal expansion and differentiation. If any of the activation requirements are detrimentally affected by ageing, immune responses will be compromised. Additionally, age-related deleterious changes in memory cells are to be expected. DC: dendritic cells; TC: T cells; Treg: regulatory T cells; CD: cluster of differentiation.

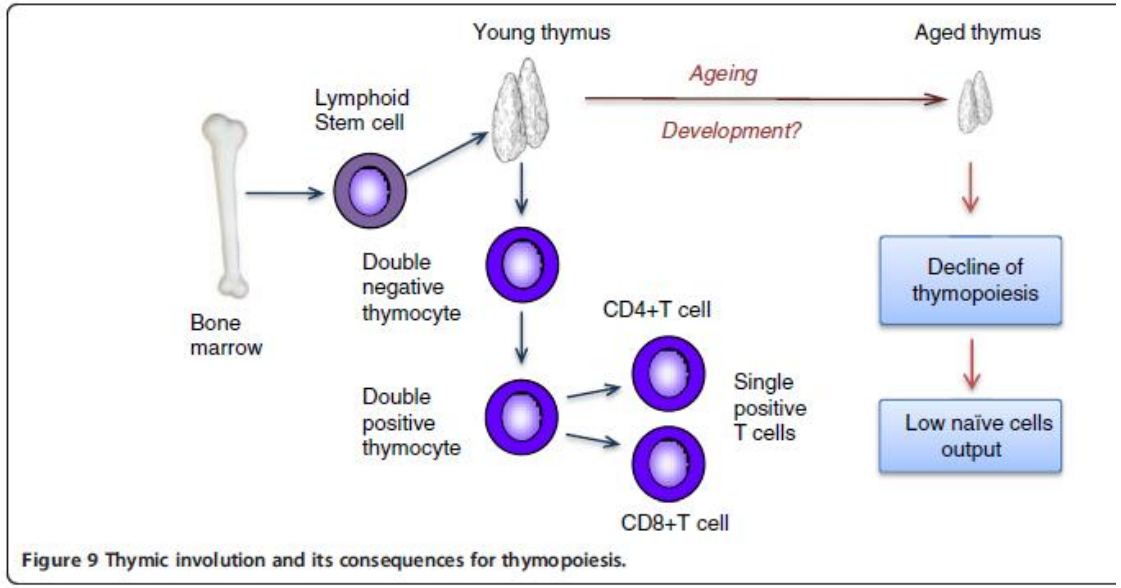


Figure 9 Thymic involution and its consequences for thymopoiesis.

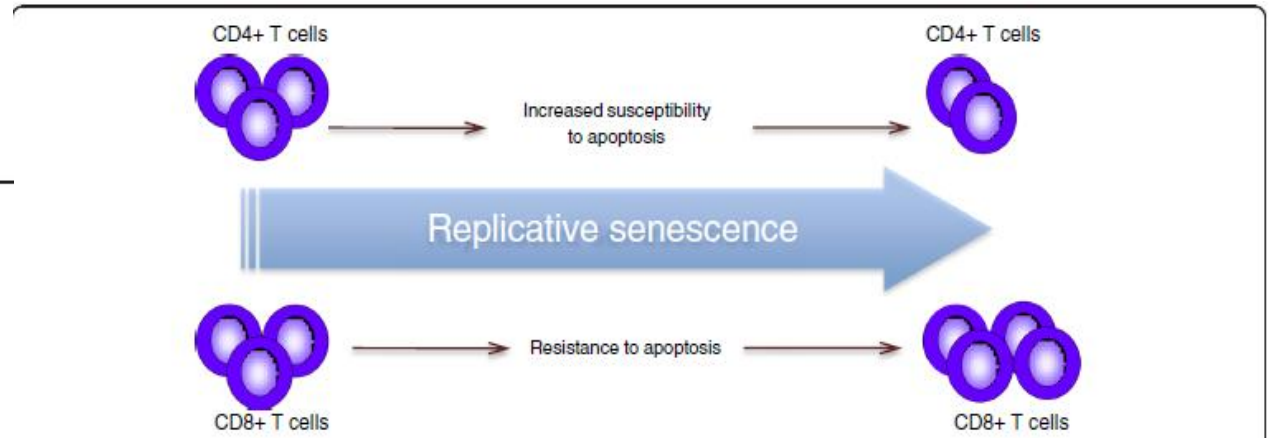


Figure 11 Accumulation of CD8-positive T cells and loss of CD4-positive T cells might be due to increased susceptibility or to acquired resistance to apoptosis of the respective T-cell subsets.

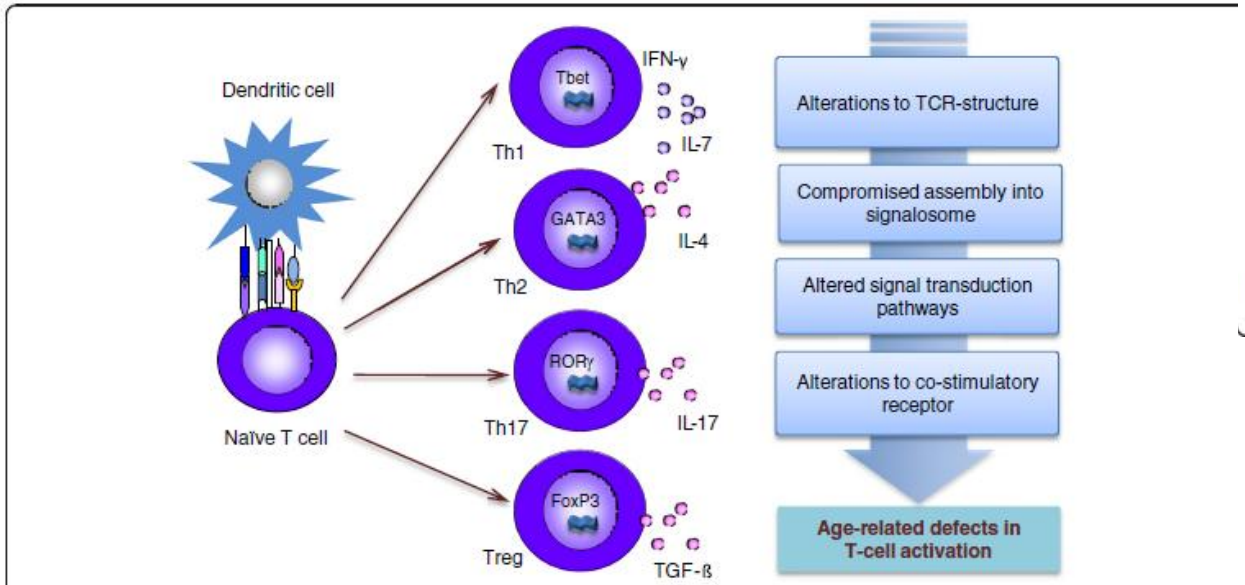
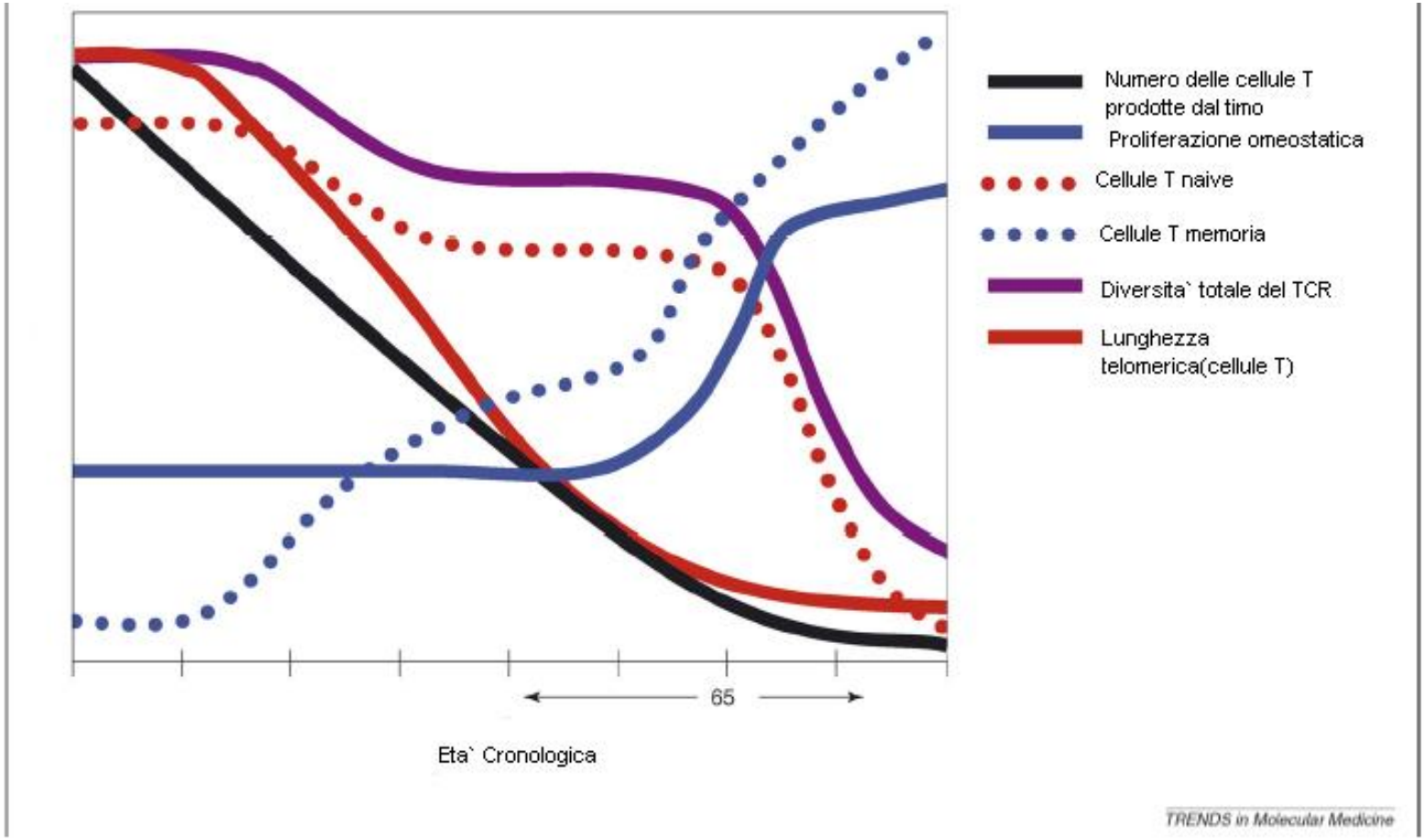


Figure 12 T-cell differentiation into functionally different T-cell subsets and age-related defects in T-cell activation. Th1: T helper 1 cells; Th2: T helper 2 cells; Th17: T helper 17 cells; Tbet, GATA3, ROR, FoxP3: different transcriptional factors; IL: interleukin; TGF-β: transforming growth factor beta.

Differential increase in aging



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Mini Review

How vaccines work on the background of the aging immune system

Laura Haynes *

Trudeau Institute, 154 Algonquin Avenue, Saranac Lake, NY 12983, USA

Table 1
Summary of NP-specific B cell responses in intact mice and in adoptive transfer model

	Intact mice[d]		Young hosts	
	Y	A	Y CD4	A CD4
B cell expansion[a]	++++	++	++++	++
GC differentiation[b]	++++	+	++++	+
Serum IgG[c]	++++	++	++++	++

[a] Expansion of NP-specific B cell population following immu

Young CD4	
Y host	A host
++++	++++
++++	++++
++++	++++

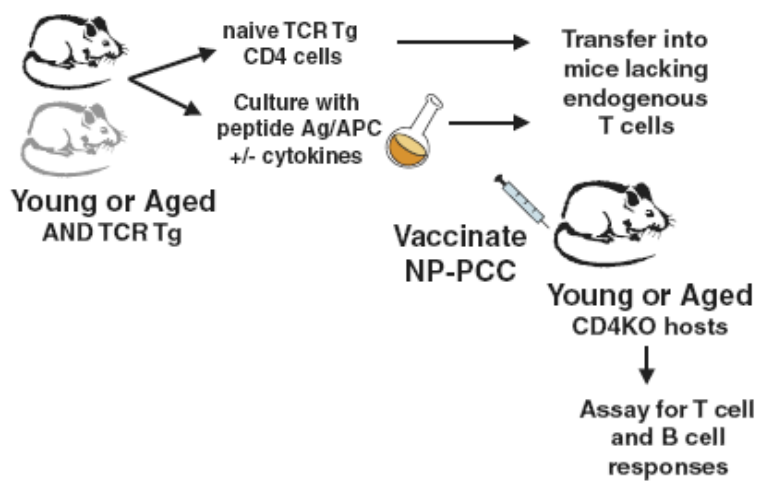


Fig. 1. Adoptive transfer model for examining CD4 cognate function. Naive CD4 T cells were harvested from young and aged AND TCR Tg

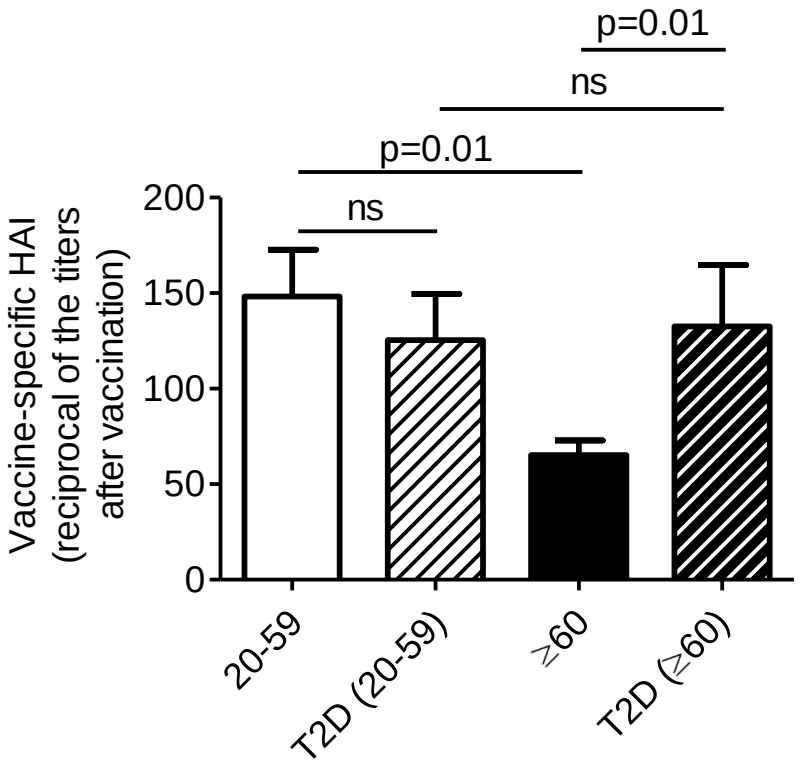
Impact of Influenza, 1990-1999

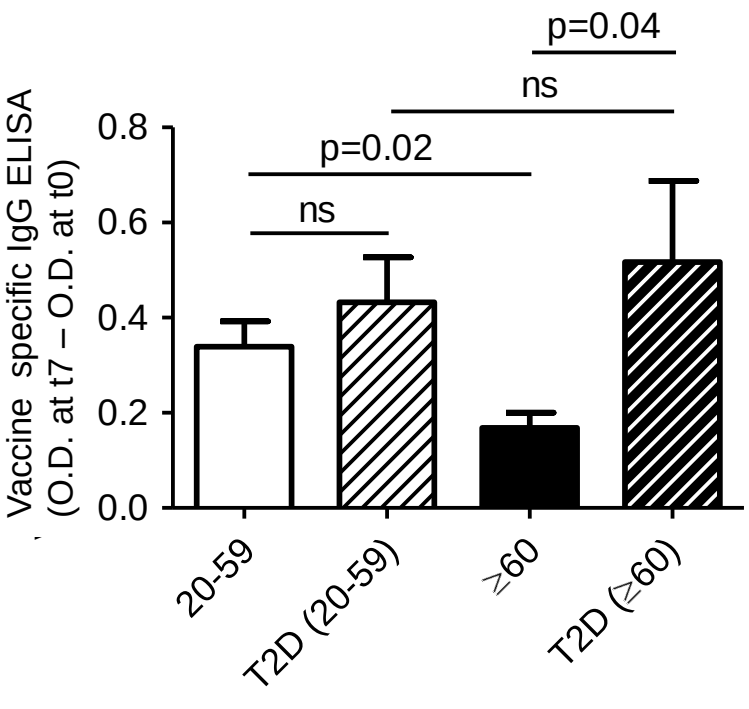
- Approximately 36,000 influenza-associated deaths during each influenza season
- Persons 65 years of age and older accounted for more than 90% of deaths
- Average of 226,000 hospitalizations during each influenza season

Inactivated Influenza Vaccine Recommendations, 2007-2008

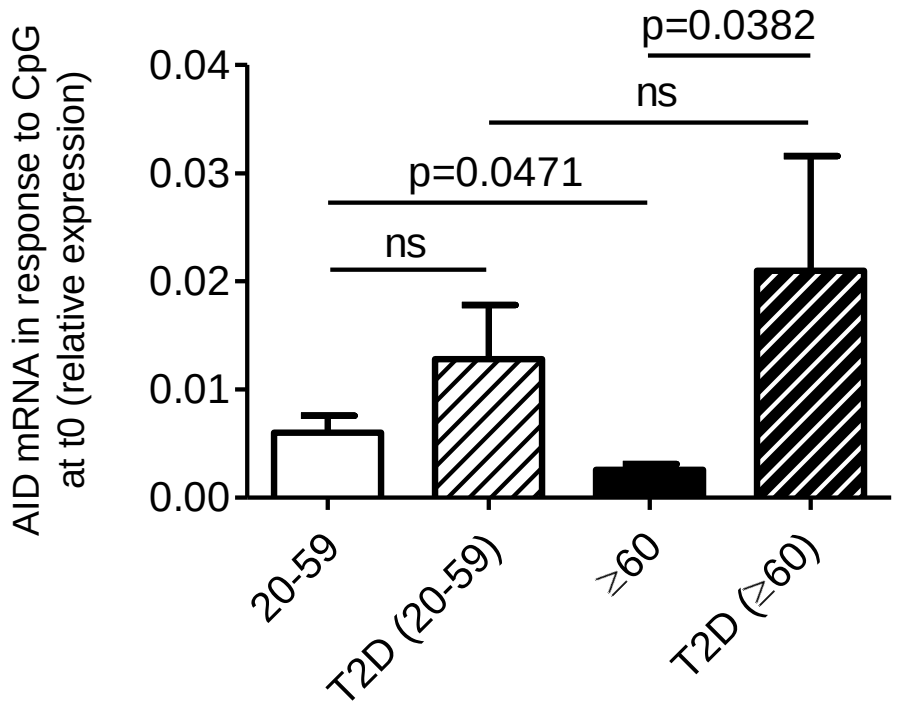
- Conditions that increase the risk of influenza complications:
  - Age
    - 65 years and older
    - 59 months and younger
  - Pulmonary (emphysema, asthma)
  - Cardiovascular
  - Metabolic (diabetes)
  - Renal dysfunction
  - Hemoglobinopathy
  - Immunosuppression, including HIV infection
  - Conditions that compromise respiratory function or increase the risk of aspiration

Serum response to influenza vaccine decreases with age in healthy, but not in T2D subjects

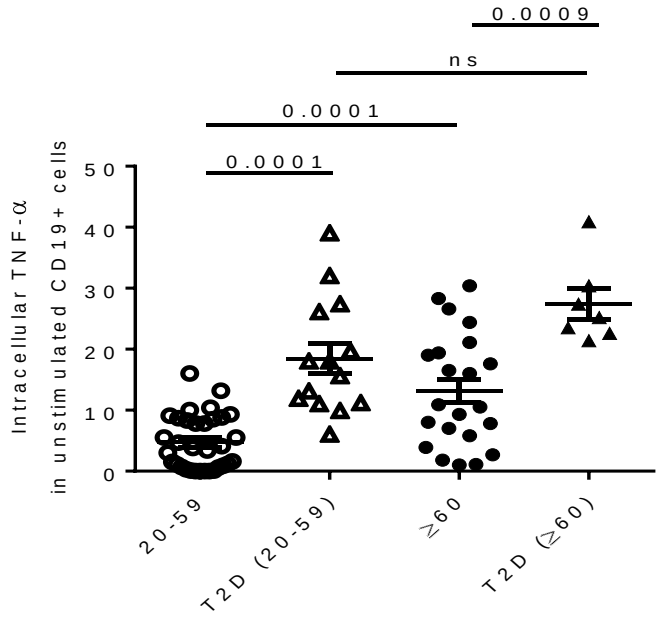




AID in vitro response to CpG is decreased with age in healthy, but not in T2D subjects



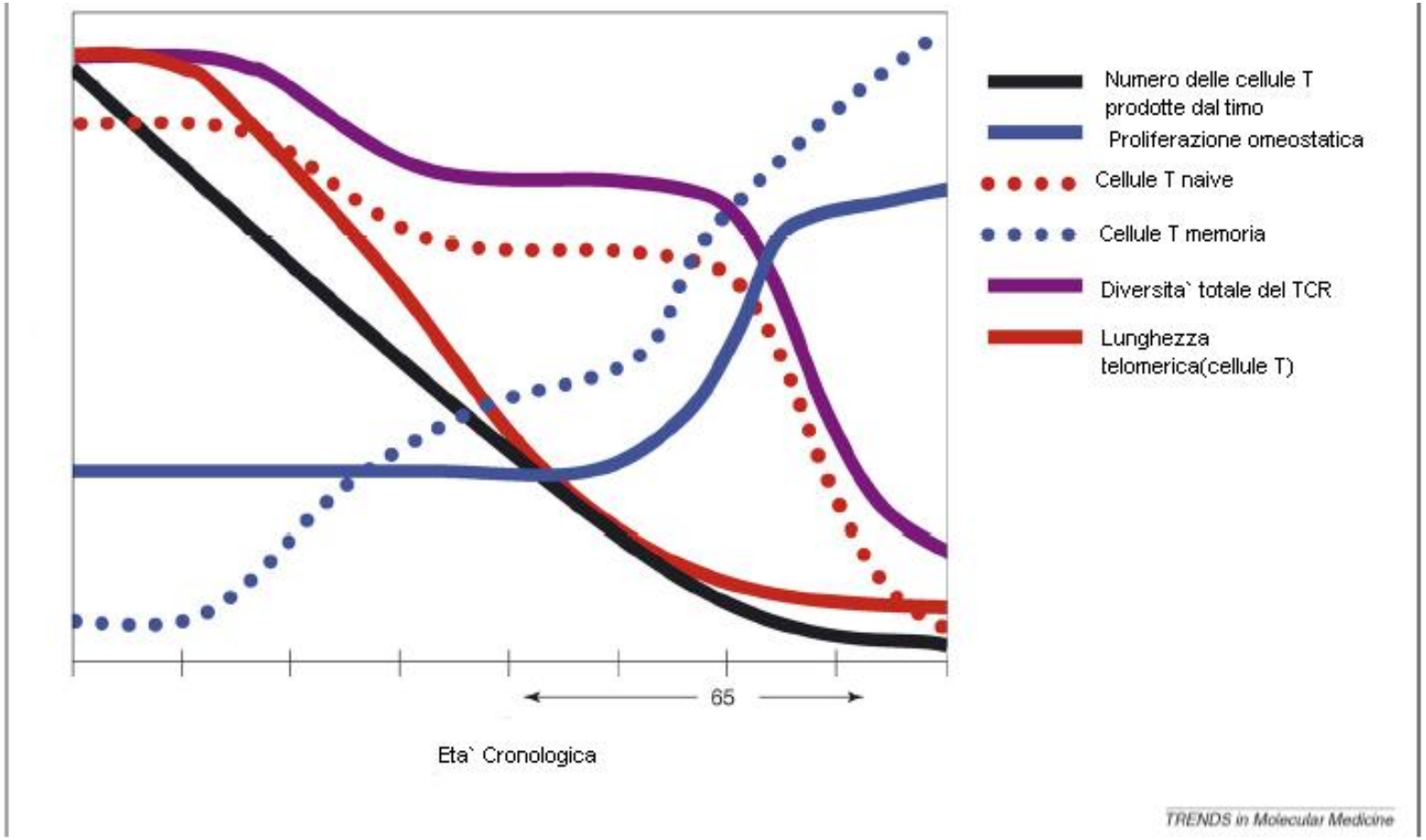
High levels of B cell-derived and systemic inflammation are present in T2D patients and in healthy elderly subjects



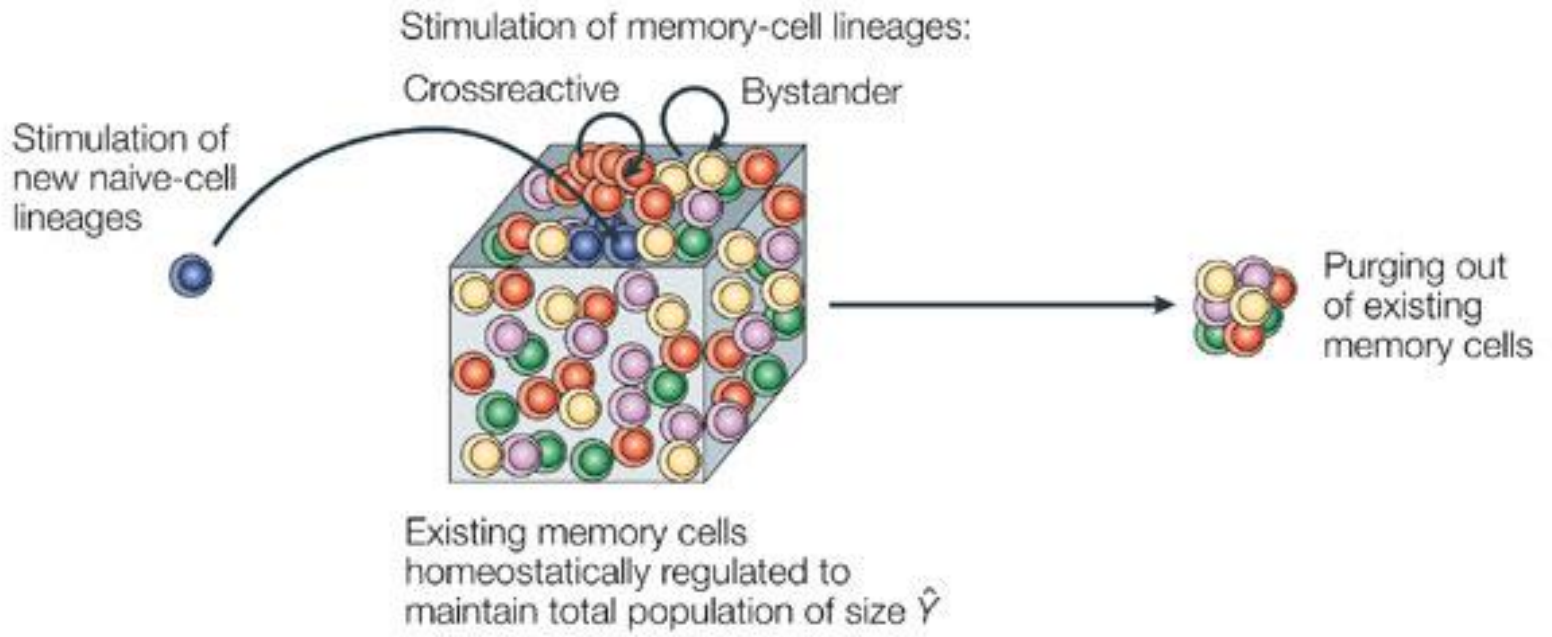
Inflammation markers in serum	Healthy young	T2D young	Healthy elderly	T2D elderly
TNF-α (pg/ml)	6 1	7 4	13 4[b]	24 16[a]
IL-6 (pg/ml)	49 22	63 69[a]	97 15[b]	170 177[a]
CRP (pg/ml)	648 91	1678 570[a]	883 63[b]	1605 114[a]

p values refer to differences between patients with diabetes and age-matched controls ([a] : p<0.05), or differences between young and elderly healthy individuals ([b] : p<0.05)

Differential increase in aging



Maintenance of immunological memory



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Towards a liquid self: how time, geography, and life experiences reshape the biological identity

Andrea Grignolio[1†], Michele Mishto[2,3†], Ana Maria Caetano Faria[4], Paolo Garagnani[5], Claudio Franceschi[1,5,6,7] and Paolo Tieri[8*]*

As a consequence, the old question whether a given molecule belongs to self or non-self looses its significance as it largely depends on the context (43), which will be here referred to as the wider perspective of the immunological biography (37).

Accordingly, by recovering the widely used sociologic metaphor advanced by Zigmunt Bauman to indicate amorphous, elusive, and rapidly changing values of contemporary Western societies (44, 45), we propose to make the final step from an ontological and static idea of self to a, *context-*, *spatial-*, *temporal-*, *inflammatory-*, *and finally process-dependent concept*, and thus introduce the hypothesis of *liquid self*.

We are beneficiaries of the advances in sanitation, disinfection, vaccination and antibiotics that have drastically reduced the incidence and mortality of infectious disease, but a dysfunctional – or simply less functional – immune system is still a major threat to its "owner". How can we preserve immune function and prevent infectious disease in the elderly?

Grazie