Immunity and ageing

Pr M de Saint-Hubert M

Immunosenescence

➢ Definition

  ✓ Decrease of immune functions associated with ageing

  ✓ Characteristics

➢ Increased risk of :

  ✓ Infections

  ✓ Inflammatory diseases (Horton…)

  ✓ Autres : AD, diabetes 2, sarcopenia,…

  ✓ Cancer?

  ✓ Auto-immunity?
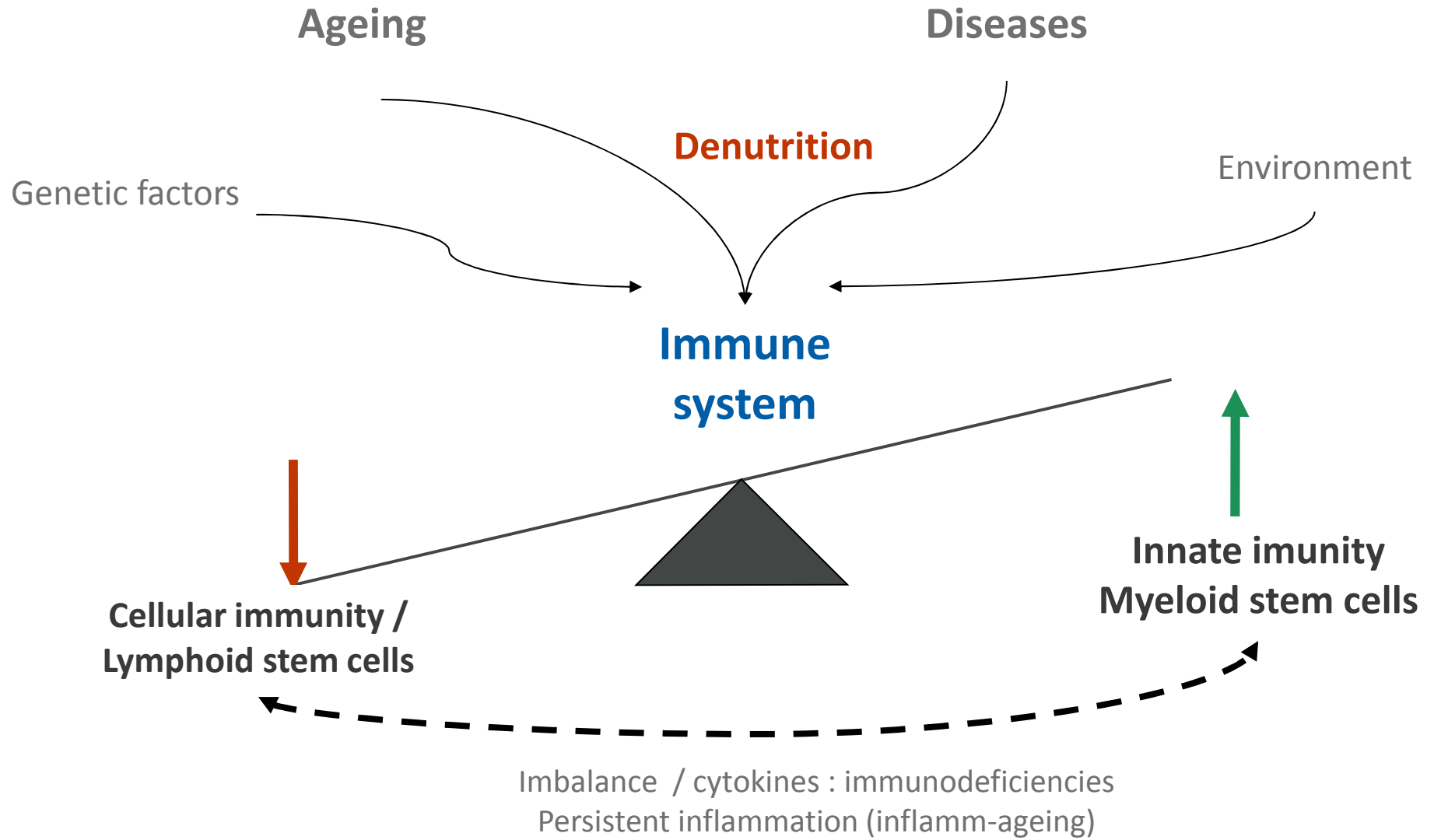
Reminder…

	Innate immunity	Adaptative immunity
Onset	Immediate	Delayed
Specificity	No	Yes
Memory	No	Yes
Vectors	Epith barriers Phagocytes Complements Cytokines	Cellular Humoral

Immunosenescence

Ageing   Diseases

Denutrition

Genetic factors   Environment

Immune system

**Cellular immunity /
Lymphoid stem cells**

**Innate imunity
Myeloid stem cells**

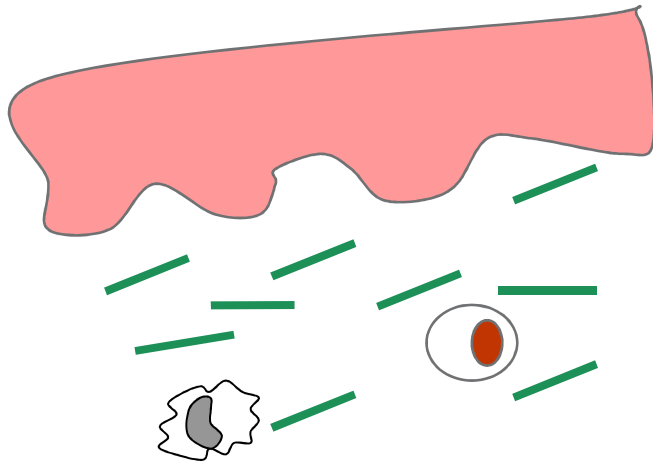Imbalance / cytokines : immunodeficiencies
Persistent inflammation (inflamm-ageing)

Innate immunity

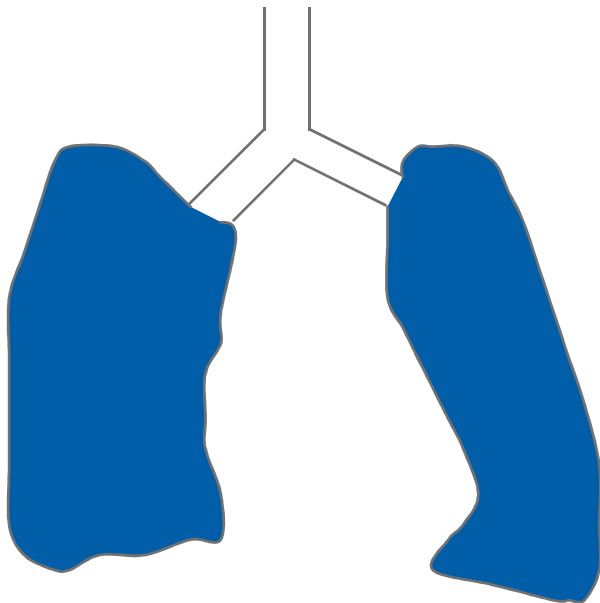## Natural barriers : anatomical et physiological changes

➤ Cutané

✓ Atrophie, sécheresse

✓ ↓ Flux sanguin

✓ Fragilité

✓ ↓ Macrophages

Innate immunity
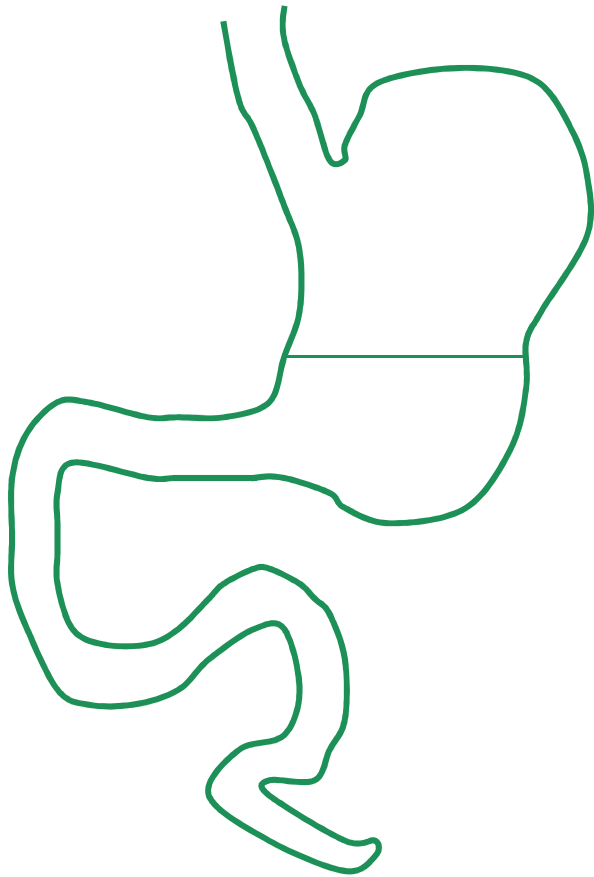## Natural barriers : anatomical et physiological changes

➤ Lung

   ✓ ↓ ciliar pouvments

   ✓ ↓ cough reflex

   ✓ ↓ local immunity

Innate immunity
Natural barriers : anatomical et physiological changes

➤ Gut

- ✓ Chronic gastric atrophy
  - ▪ Achlorhydria (IPP!!)
  - ▪ HPylori
- ✓ ↓ mucosal IgA
- ✓ Constipation
- ✓ Microbiote
  - ▪ AB!!!

Intestinal microbiota

➢ Increasing inter-individual variation with age

➢ Faecal microbiota composition

✓ Community (n=83), LTF (n=60), rehabilitation (n=15), hospital, out-patients (n=20)

➢ Results:

✓ Correlation with residence location

✓ Correlation with diet (questionnaire)

  ▪ Food diversity index: correlation with microbiota diversity index

✓ Correlation between residence & diet!!

  ▪ LTC >< CD : more fat, low fiber

✓ Correlation with « frailty »
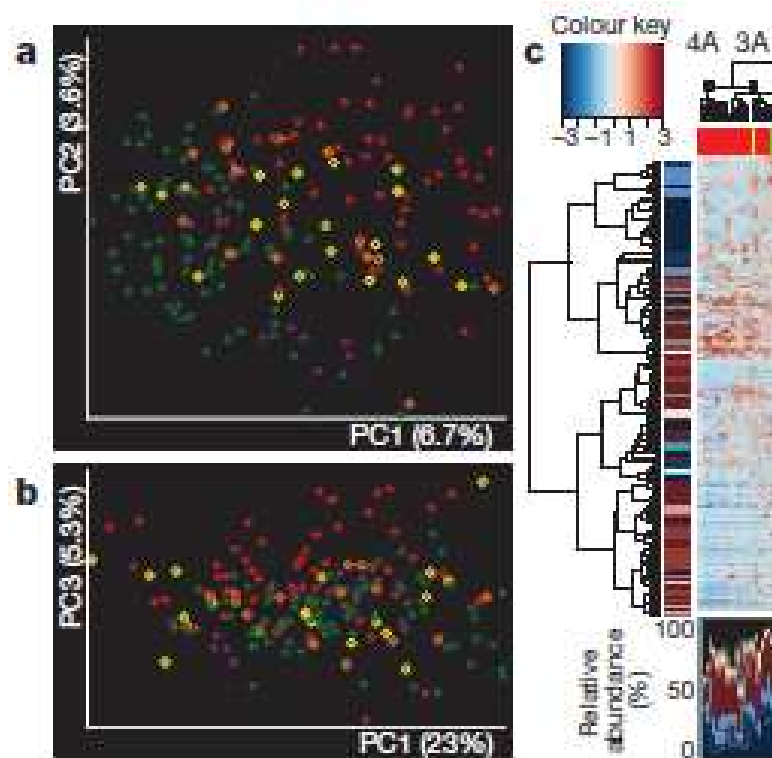
Claesson et al, Nature 2012

Figure 1 | Microbiota analysis separates elderly subjects based upon where they live in the community. a, Unweighted and b, weighted UniFrac PCoA of faecal microbiota from 191 subjects. Subject colour coding: green, community; yellow, day hospital; orange, rehabilitation; red, long-stay; and purple, young healthy control subjects. c, Hierarchical Ward-linkage clustering based on the
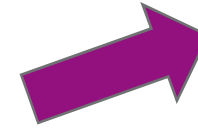
Innate immunity

Natural barriers : anatomical et physiological changes

> Urinaire

- ✓ ↓ vesical capacity
- ✓ ↓ urinary flow
- ✓ ↓ Acidification & cc
- ✓ ↑ bacterial adherence
- ✓ Prostatic hypertrophy
- ✓ Hormonal changes (E2)
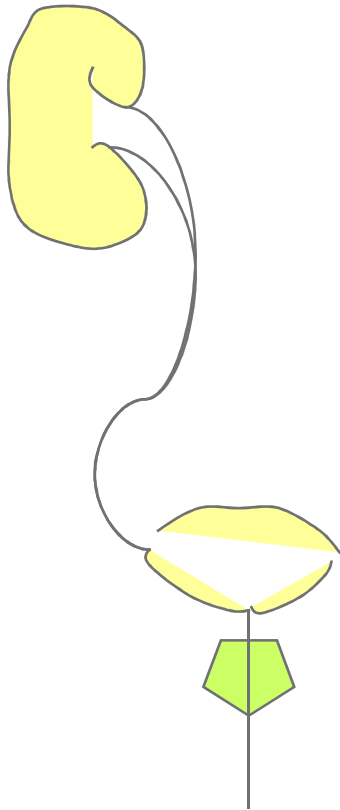
Innate immunity

➢ Polynuclear cells, monocytes and macrophages

  ✓ Decreased phagocyte and bactericidal functions

  ✓ Decreased signalisation pathways & feed back

➢ Cellules Natural Killer

  ✓ Compensation : ↑ number

  ✓ ↓ Function (légère)
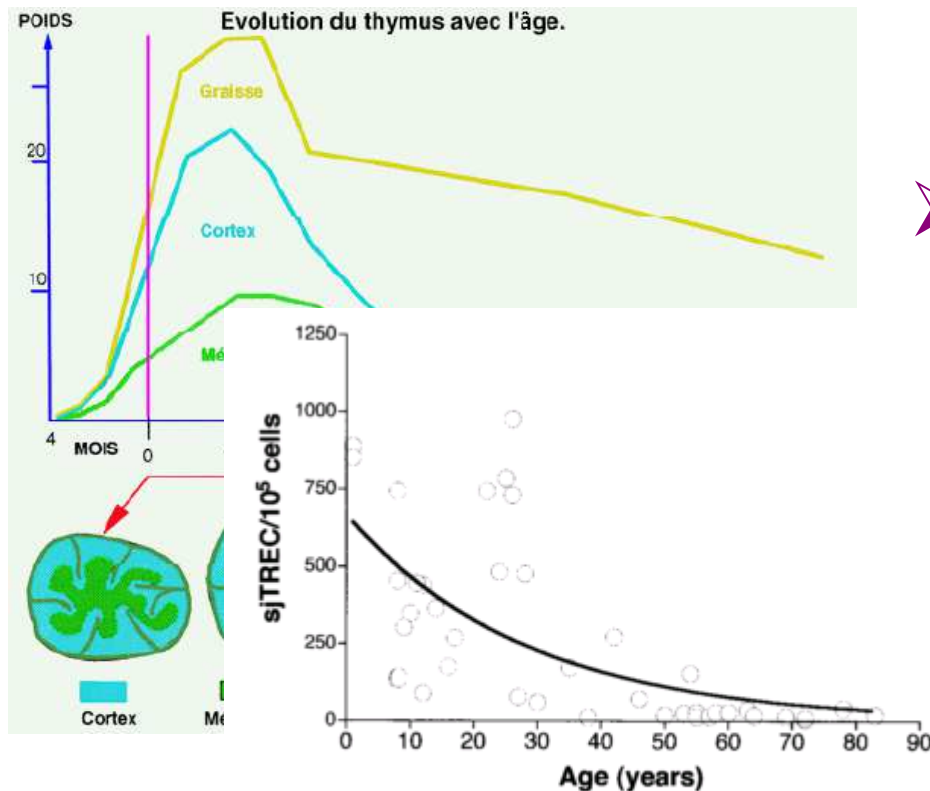
Adaptative immunity: cellular

Figure 2 Age-related evolution of sjTREC number per 100 000 T cells in normal subjects ($n=41$). The number of sjTRECs was

- ➤ Decreased central production of naive T cells
- ➤ Thymic involution
  - ✓ Self-tolerance
  - ✓ Diversity of repertory of T Cells receptor
  - ✓ Role of GH & IGF-1!

Geenen et al, J Endocrinol 2003

Adaptative immunity: cellular

- ↓ peripheral naives T cells
- ↓ diversity of T cell receptor repertory
- ↓ memory T cells
- Oligoclonal expansion of memory T cells with poor function
  - ✓ Role of chronic (viral) infections
    - CMV
  - ✓ Immunological filling
    - Recruitment of naives cells

Adaptative immunity: humorale

➤ ↓ progenitors of B cells

➤ Antibodies :

✓ Changes in Ab repertory

✓ ↓ production

✓ ↓ switch : IgM > IgG

✓ ↓ affinity, lower protection

✓ ↑ Auto Ab (few csq)

✓ ↑ MGUS

▪ <1% < 60 y → 20% > 90 y

Inflammation and ageing
Inflamm-ageing

➢ Ageing:
- ✓ Chronic low-grade inflammation

➢ Causes
- ✓ Imbalance between inflammatory (IL-6 & co) and anti-inflammatory (IL-10 & co) networks
- ✓ Déficits hormonaux (E2)…
- ✓ Autres : polymorphismes génétiques, tabac, obésité, HT,…

Franceschi et al, Mech Ageing Dev 2006
Pawelec et al., Immunol Rev 2005;205:257-268
Ershler W et Keller E, Annu Rev Med 2000;51-245-270

Inflammation

Exclusion symptoms or diseases (SRH, smoking…),
treatment associed with increased CRP ou dependance of ADL

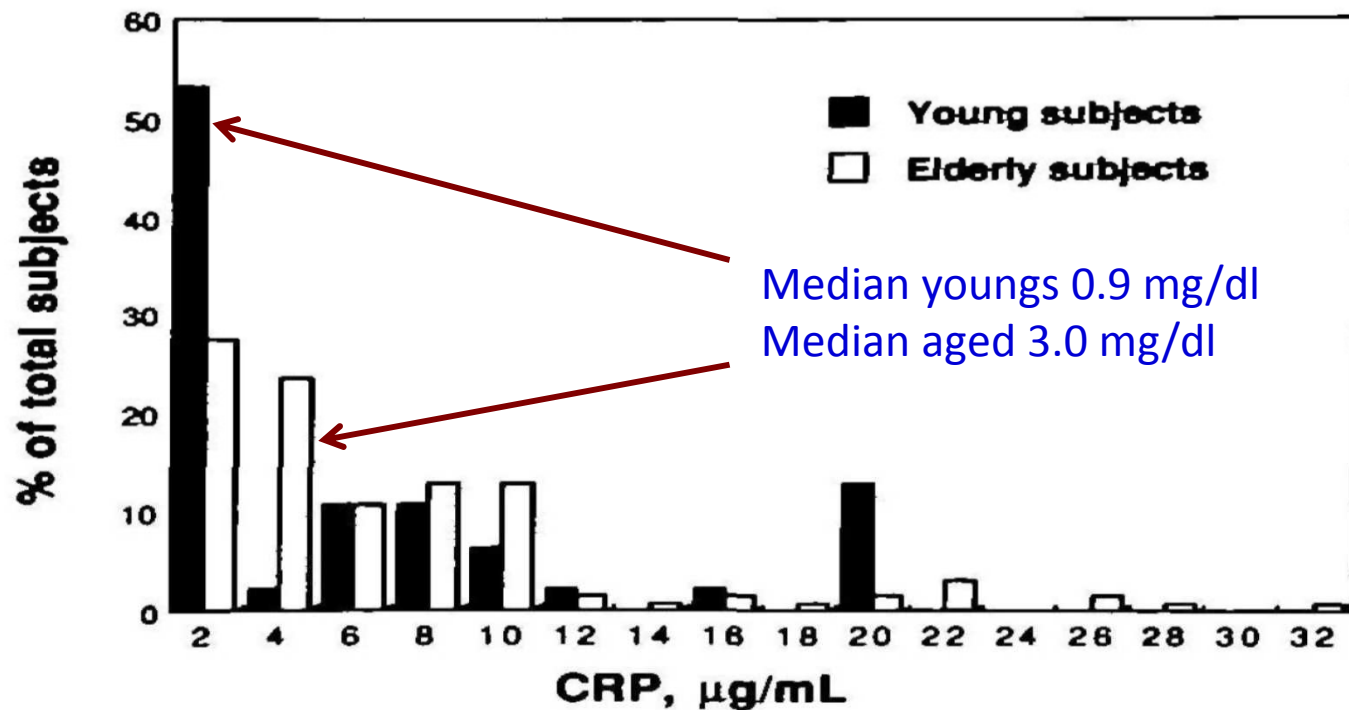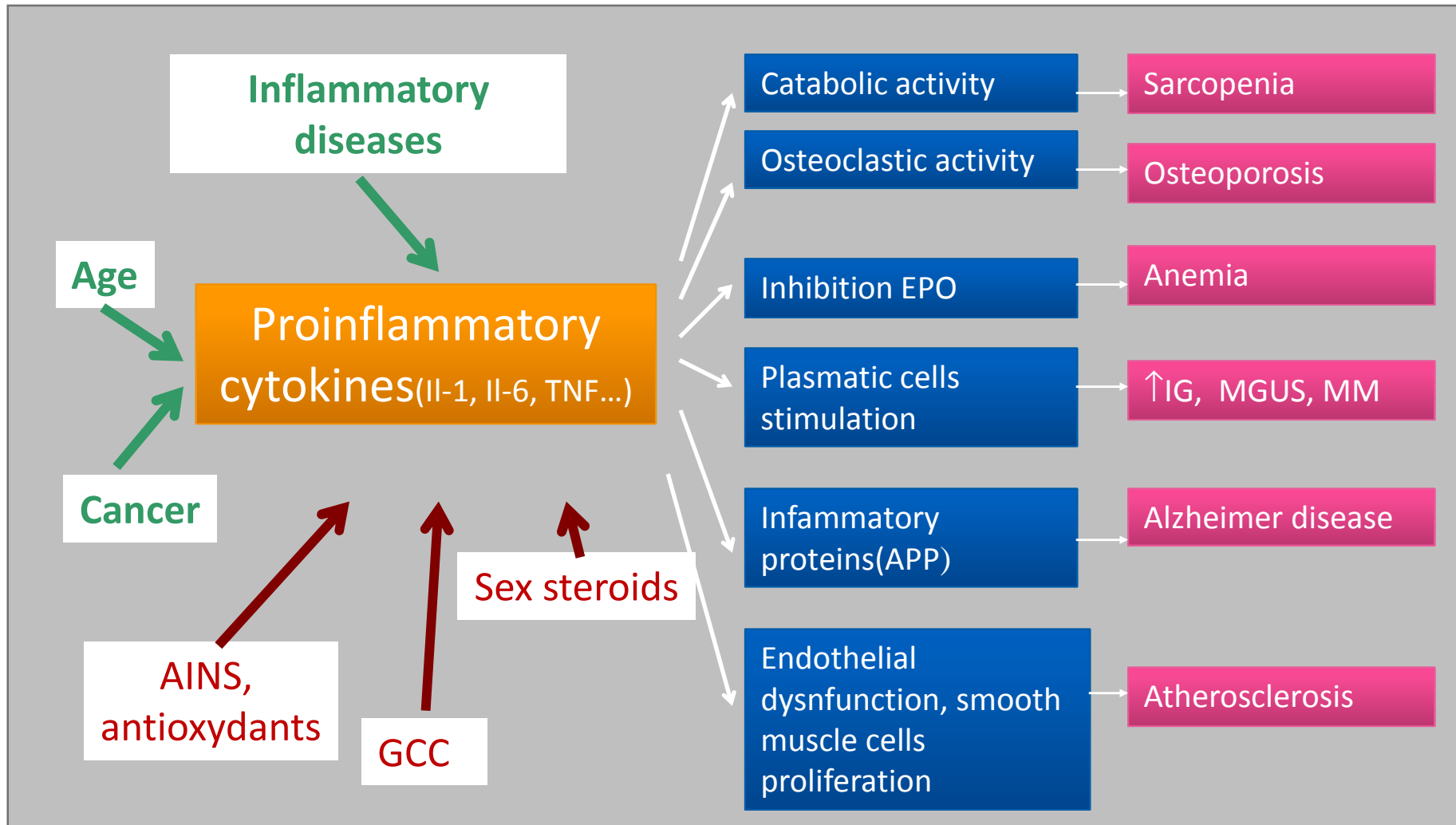Median youngs 0.9 mg/dl
Median aged 3.0 mg/dl

Figure 2. Distribution of serum CRP concentrations in 131 healthy elderly individuals and 47 young subjects as quantified by ELISA. The population distributions are significantly different, $p = 0.0003$.

Ballou et al, Age Ageing 1996;25

Proinflammatory cytokines & frailty
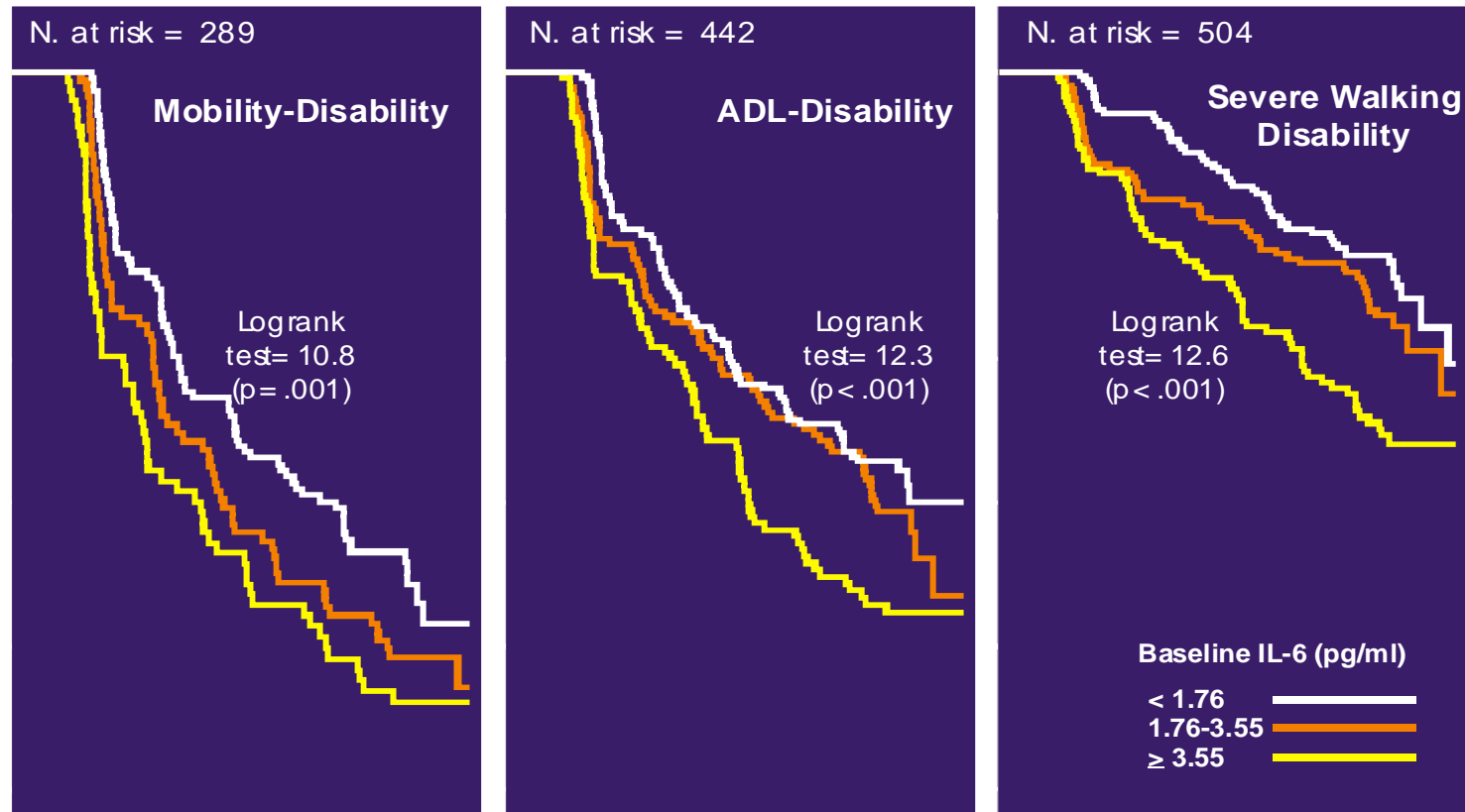

CHU UCL NAMUR

Inflammation

➤ Cross-sectional studies:

   ✓ Inflammation : cause or consequence?

➤ Longitudinal studies

   ✓ Il-6, TNF- α, CRP :

- Mortality
- Dependance, mobility
- Frailty

Bruunsgaard H et al, Immunol Allergy Clin N Am 2003
Cohen et al, Am J Med 2003;114
Ferrucci et al, JAGS 1999;639-646

Il-6 Serum Level and Risk of New Disability in Frail Older Women (WHAS)

N. at risk = 289

Mobility-Disability

Logrank test= 10.8 (p= .001)

N. at risk = 442

ADL-Disability

Logrank test= 12.3 (p< .001)

N. at risk = 504

Severe Walking Disability

Logrank test= 12.6 (p< .001)

Baseline IL-6 (pg/ml)

< 1.76
1.76-3.55
≥ 3.55

Ferruci L et al, JAGS 2002;50

Immune Risk Profile (IRP)

➤ Correlated with mortality

    ✓ Predicted 97% of survival

➤ Characteristics:

✓ CD 4 < CD8

✓ Poor proliferative response T cells

✓ ↑ CD8+ CD28- CD57-

✓ Low naive cells

✓ ↓ B cells

✓ CMV seropositivity

Healthy ageing in immunity:
The SENIEUR protocol

Goal : distangle effects of comorbidites and ageing in immunity

<div style="border">

- ➤ No infection < 6 W
- ➤ No infl < 6 W
- ➤ No vaccine < 6 W
- ➤ No cancer
- ➤ No immunomodulator
- ➤ No NSAID / SAID
- ➤ No medication for chronic disease

</div>

<div style="border">

- ➤ Strict normality
  - ✓ Glycemia
  - ✓ Urinary spot
  - ✓ Hepatic enzymes
  - ✓ Urea / renal function
  - ✓ Hemoglobine
  - ✓ VS
  - ✓ Lymphocytes
  - ✓ Eosinophiles

</div>

Ligthart et al, Mech Ageing Dev 1984

Healthy ageing in immunity: SENIEUR protocol

- No infection < 6 W
- No infl < 6 W
- No vaccine < 6 W
- No cancer
- No immunomo...
- No NSAID...
- N... for chronic di...

- Strict nor...
- ...ry spot
- Hepatic enzymes
- Urea / renal function
- Hemoglobine
- VS
- Lymphocytes
- Eosinophiles

Not a geriatric patient!!!

Selection of (supra) normal individuals...

Ligthart et al, Mech Ageing Dev 1984

Conclusions of SENIEUR
Age is not all…

➢ « Very healthy elderly have only modest changes in immune response »

➢ Impact of age :

  ✓ Replicative senescence

  ✓ Thymic involution and T cells dysfunction

➢ Better knowledge of immunity and ageing

➢ Time for a paradigm shift…

Castle et al, Mech Ageing Dev 2001

Marik PE et al, JAGS 2001 ;49:5-9
Age is not associated with a decline in circulating levels of cytokines during septic shock.

Bruunsgaard H et al, J Inf Dis 1999;180:551-4
Elderly humans show prolonged in vivo inflammatory activity during pneumococcal infections.

Castle SC et al, Mech Ageing Dev *2001;122:127-140*
Very healthy elderly only have modest changes in immune function (SENIEUR).

Robust

Frail
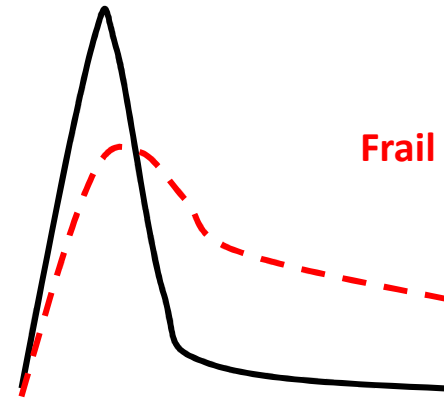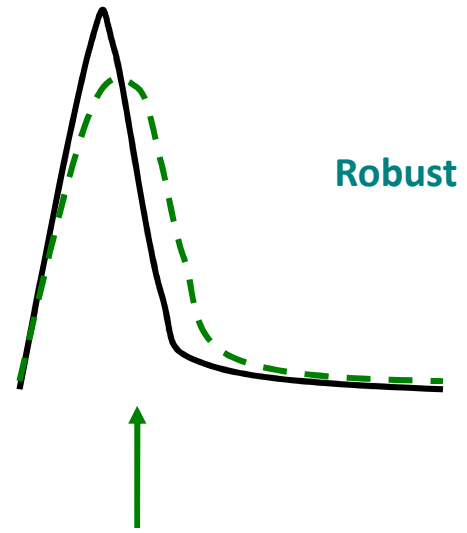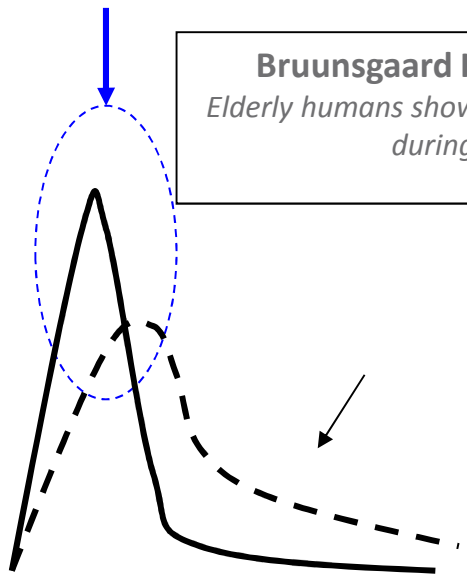
——— Young patients

- - - - Aged patients

Comorbidites

➢ Influence the immune responses

 ✓ Correlation between immunity (proliferative response LyT / cytokines production*)et level of comorbidity

 ✓ Increase with age

 ✓ Diabetes, BPCO, heart failure…

 ✓ Impact on infection

➢ Interaction with organ senescence

Castle SC et al, JAGS 2005;53:1565-1569

Influence of nutrition of immune functions

➤ Successful ageing (primary immune ageing) - SENIEUR
  - ✓ Changes in T-cell subsets but not in T-cell function

➤ Common ageing (secondary immune ageing)
  - ✓ Influenced by micronutrient deficits --> nutritional supplements.

➤ Pathological ageing (tertiary immune ageing)
  - ✓ Immune responses strongly related to nutritional status.
  - ✓ Decreased immune responses → long-lasting acute-phase responses → greater use of nutritional reserves during disease → increased frailty.

Malnutrition ⇄ Infection

Lesourd B, Proc Nut Soc 2006
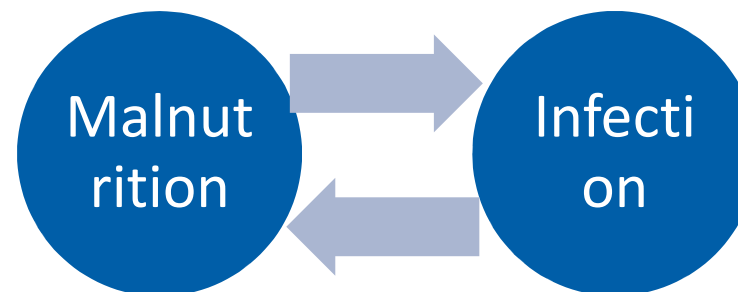
Denutrition

➢ Characteristics
- ✓ Hypoalbuminemia
- ✓ Folates, B12
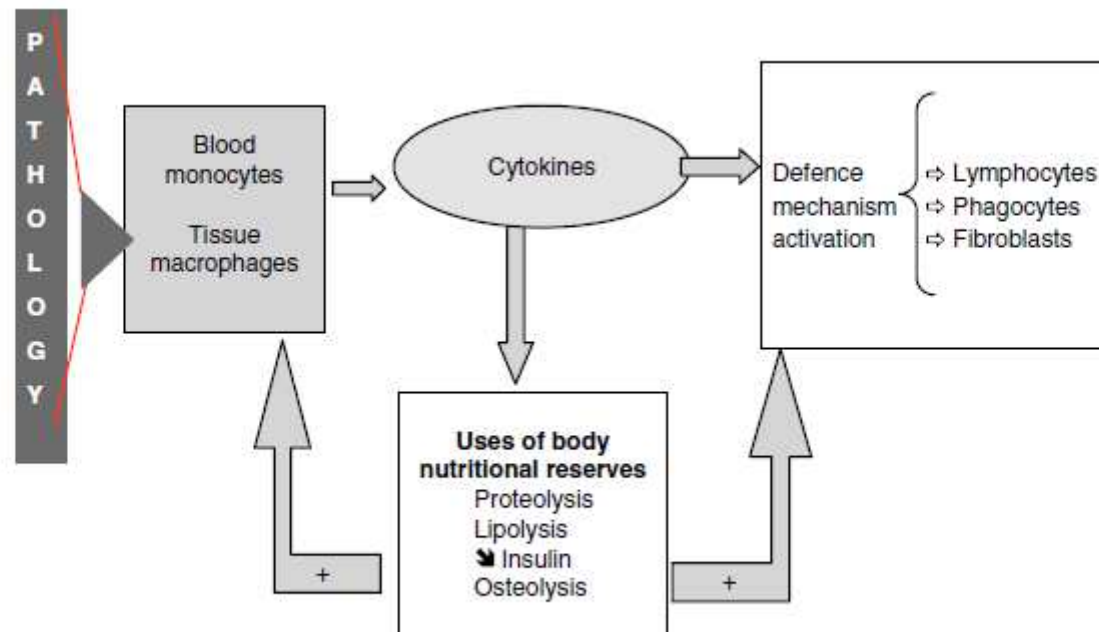- ✓ Micronutriments : Fer, Zinc,...

Fig. 1. Nutrition and disease. The body's response to stress and the relationship with body nutrient reserves. +, Body reserves are used to enhance defence mechanisms and macrophage metabolism; ↘, insulin secretion decreases.

Lesourd B, Proc Nut Soc 2006

Dietary influence on the aged immune response

➢ Micronutriments

   ✓ Vitamine E (anti-oxidant)

      ▪ enhance T cell functions by directly influencing membrane integrity

   ✓ Zinc

      ▪ immune cell proliferation, cytokine production, and specific reductions in NK cell activity and neutrophil function

   ✓ Carotenoids

      ▪ Enhance immune response, bactericidal activity

➢ Probiotics

**Low / limited evidence
of supplementation**

Maijo et al, Mech Ageing Dev 2014

Dietary influence on the aged immune response

- Polyphenols
- Macronutriments : essential fatty acids
- Iron (neutrophil, cellular imm)
- Whole diet approach :
  - Mediterranean diet
  - Influence cellular and circulating levels of inflammatory biomarkers related to atherogenesis
  - NU-AGE : randomized study in Europe (on-going)

Maijo et al, Mech Ageing Dev 2014
Berendsen et al, Mech Ageing Dev 2014

So what...

CLINICAL IMPACTS OF IMMUNOSENESCENCE

Inflammation : consequences

- Infections

- Alzheimer disease

- Atherosclerosis et CV diseases

- Diabete 2 (insulinoresistance)

- Sarcopenia

Bruunsgaard H et al, Immunol Allergy Clin N Am 2003

Systemic infection & inflammation :
Neurodegenerative csq?

➢ Long-term intake of NSAID : protection >< AD
  - ✓ Lower incidence

➢ Delirium :
  - ✓ $\uparrow$ risk for dementia
  - ✓ Similarities: !! ΔΔ !!!
  - ✓ Same physiopathology ?

➢ $\uparrow$ risk AD following infections (retrospect)
  - ✓ Inflammmation and alteration fo microgliocytes

➢ Before diagnosis :
  - ✓ Increased CRP, Il-6 (5 y before)

Perry VH et al, Nature Reviews, Imm 2007;4:161-167

Sickness behaviour

➢ General
  ✓ Lethargia
  ✓ Anhedonisme
  ✓ Apathy
  ✓ Decreased social interactions
  ✓ Poor concentration

➢ Homeostatic mechanism allowing an adaptation against infection/ inflammation
  ✓ Microbial replication

➢ Frequent in AD

Perry VH et al, Nature Immunol 2007;7:161-167

Prevention & treatments?

Target	Action	
Stem cells	Preserve telomers Increase lymphoid precursors	Telomerases?? Antioxydants
Thymus	Increase thymic output	**GH, IGF-1**
	Peripheral naives T cells	IL-7
Inflamm-ageing	inflammation	AID? Caloric restriction? Vaccination Rapamycine (CMV)
ALL?		**Nutrition**
Innate immunity	Microbiota	Probiotics

Adapted from a presentation of Prof. Carcelain, Paris, 2026

Physical exercise /training

➤ ↓ CV diseases incidence

➤ Confondants : age, smoking, BMI

➤ Acute :

   ✓ Transient increase in acute-phase proteins

➤ Chronic : ↓ inflammation (Cross-sect + longit studies)

   ✓ ↓ cytokines production (adipose tissues, musse, neutrophils)

   ✓ Endothelial functions

   ✓ Anti-oxidant effects

Nutrition

- Impact of supplementation (heterogeneous)
- Whole diet supplementation (NU-AGE)
- Prevention I, II, III

NLR: Neutrophil Lymphocytes Ratio

➤ Lymphopenia (<1100): risk predictor for mortality?

  ✓ Geriatric department

➤ Neutrophil lymphocyte ratio (NLR)

  ✓ Hip fracture & mortality

  ✓ Inflammation

  ✓ Cardiovascular risk

  ✓ Cancer

Deschasse et al, Geriatr Neurops Vieill 2014
Forget et al, BMC Res Notes 2016

55-70 ans	
-Tetanos-dipht-coquel ou Td -Influenza	-Pneumococcal vaccine -HZ
1x/y after retirement	**Wounds**
- Influenza	-Tetanos
Hospitalisations	**NH admission**
- Pneumococcal vaccine	-Td or TT -Influenza -Pneumococcal vaccine

Conclusion

➢ Immunosenescence : desequilibrum

    ✓ Innate immunity > adaptative immunity

    ✓ Cellular immunity (Ly T)

    ✓ Complex mechanisms

    ✓ Chronic low-grade inflammation

➢ Various impact according health status

➢ Perspectives for therapeutic targets…