IMMUNITY AND THE AGING BRAIN

Sonya Vasto
www.immunityageing.com

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We Now Live Twice As Long As We Did 150 Years Ago

Akbar A et. al. (2004): Nature Reviews | Immunology
Come descritto da Gompertz, i tassi di mortalità aumentano esponenzialmente con l’età con un raddoppio durante la vita adulta della mortalità ogni 8 anni. Ad età più avanzate il tasso rallenta come indicato dal punto fuori la linea; questo fenomeno è stato chiamato selezione demografica (vedasi testo).
Immunity, Ageing and Longevity

Relevance of immune system

*Both infectious and inflammatory diseases are increased in frequency and severity in the elderly*

<table>
<thead>
<tr>
<th>Increased frequency</th>
<th>Relative risk of mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular diseases</td>
<td>100</td>
</tr>
<tr>
<td>Chronic pulmonary diseases</td>
<td>100</td>
</tr>
<tr>
<td>Acute pulmonary diseases</td>
<td>89</td>
</tr>
<tr>
<td>Cancer</td>
<td>43</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>10</td>
</tr>
</tbody>
</table>
Rate of death from infectious disease continues to accelerate with age

Causes of death
(Japanese females)

From Horiuchi & Wilmoth, J Gerontol, 1997
Bacterial infections have an increased frequency in the elderly population

- respiratory infections
  - bronchitis
  - pneumonia

- digestive tract infections
  - antibiotic-associated diarrhea
  - diverticulitis

- skin and soft tissue infections
  - cellulitis
  - diabetic foot infection

- infectious endocarditis

- tuberculosis

- urinary tract infections
  - cystitis
  - pyelonephritis

- foreign body infection
  - endoprothesis
  - indwelling catheters

- influenza

These data suggest a key role for clonotypic and innate immunity in the control of the survival of the elderly, because resistance to these diseases depends, at least in part, on a well-functioning immune system.
Ageing

Aging is a post-maturational process that, because of a diminished homeostasis and increased organism vulnerability, causes a reduction of the response to environmental stimuli.

Inflamm-ageing can thus be considered the main driving force for major age-related diseases and the evolutionary price to pay for an immune system fully capable of defending against infectious diseases at younger, reproductive age.
Ageing

**Endocrine function**
The body’s system of glands, which secrete helpful chemicals into the blood, becomes less efficient with time.

**Brain function**
Many changes occur in brain cells and function over time.

**Cardiovascular health**
The heart weakens with age and the network of arteries can accumulate deposits.

**Glucose regulation**
With age, some people develop diabetes, a disease involving an insulin deficiency and a loss of ability to regulate sugar.

**Muscle and skeletal health**
Muscles atrophy and bones weaken with age.

**The immune system**
The natural system of defenses mounted by the body to combat foreign organisms begins to let down its guard as we grow old.

**Oxidative stress**
Life-giving oxygen, paradoxically, can be bad for health. Oxygen sometimes manifests itself as free radicals, toxic ionized oxygen molecules that roam the body.
Immunosenescence
from the evolutionary point of view

• Subject to evolutionary constraints
• Humans lived 30-50 years a couple of centuries ago. Nowadays, they lives between 80-120 years. This is longer than predicted
• Antigenic burden encompassing decades of evolutionary unpredicted exposure
• The evolutionary recent defence mechanisms deteriorate with age
Immunosenescence
from the evolutionary point of view

• Antagonistic pleiotropy: natural selection has favoured genes conferring short-term benefits at the cost of deterioration in later life
• IS has probably been selected to serve individuals only until reproduction. After that, biochemical processes proceed freely without past selective pressure to improve the life of an individual
• Thymic involution in early age supports these hypothesis
Immunosenescence

- Thymus involution
- Telomere shortening
- Oxidative stress
- Chronic infections
- Autoimmune diseases
- Decreased T cell function
- Increased inflammatory activity
- Dementia
- Atherosclerosis
- Type II diabetes
- Osteoporosis
INFLAMMATION

It’s the basic way in which the body reacts to infection, irritation or other injury.

The reaction that occurs in the tissues in response to an injury or an abnormal stimulation caused by a physical, chemical, or biologic substance.
CHRONIC INFLAMMATION:
stable low grade irritation that continuously damages the tissue

Two switches are involved in the development of persistent chronic inflammation

*Expert Reviews in Molecular Medicine ©2002 Cambridge University Press*
Coordinated gene regulation during systemic inflammation.

On the site of infection or injury, infiltrated immune cells are activated and secrete proinflammatory cytokines. These cytokines then activate transcription factors, such as Stat3, NFκB, or C/EBPβ, and cooperatively regulate gene expressions of acute phase proteins in the liver. Over 7% of total mouse genome was mobilized by bacterial protein, LPS.
Age-Related Inflammation: the Contribution of Different Organs, Tissues and Systems. How to Face it for Therapeutic Approaches

E. Çevenini\textsuperscript{1}, C. Caruso\textsuperscript{2}, G. Canò\textsuperscript{3}, M. Cappi\textsuperscript{4}, D. Nuzzo\textsuperscript{3}, G. Durò\textsuperscript{3}, C. Rizzo\textsuperscript{2}, G. Colonna-Romano\textsuperscript{2}, D. Lio\textsuperscript{2}, D. Di Carlo\textsuperscript{3}, M.G. Palmis\textsuperscript{1}, M. Scurti\textsuperscript{1}, E. Pini\textsuperscript{1}, C. Franceschi\textsuperscript{1} and S. Vasto\textsuperscript{2}

\[ \text{ADIPOSE TISSUE} \quad \text{LIVER} \]
\[ \text{GUT MICROBIOTA} \quad \text{IMMUNE SYSTEM} \quad \text{MUSCLE} \]

\textbf{INFLAMM-AGEING}
(Circulating molecular mediators)

Site-restricted inflammation:
- brain → dementia; 
- liver → hepatitis, cirrhosis; 
- muscle → sarcopenia; 
- adipose tissue → obesity

(...)

Systemic inflammation:
- frailty, CVD and atherosclerosis, cancer

(...)

\textbf{ANTI-INFLAMMATORY REGULATORS}
The immune system

INNATE

NK cells

INSTRUCTIVE

B cells
(humoral via antibodies)

T cells
(cellular effectors; cytokines)

antigen-presenting cells

phagocytes

dendritic cells

Inflammation
## Ageing and innate immunity

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Preserved</th>
<th>Reduced</th>
<th>Increased</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophil</td>
<td>Phagocytosis, TLR2, TLR4 expression, GM-CSFR expression</td>
<td>Superoxide production, Chemotaxis, Apoptosis, Signal transduction, Molecule recruitment into lipid rafts</td>
<td>PGE2 production</td>
</tr>
<tr>
<td>Macrophage</td>
<td>Number</td>
<td>Phagocytosis, Superoxide production, Chemotaxis, Apoptosis, TLR expression, Signal transduction, Cytokine production, MHC class II expression</td>
<td></td>
</tr>
<tr>
<td>Dendritic cell</td>
<td>Antigen presentation (decreased in frail elderly)</td>
<td>Number of Langerhans cells, Langerhans cell migration</td>
<td>Per cell cytotoxicity, Signal transduction, Response to cytokines, Cytokine production</td>
</tr>
<tr>
<td>NK cell</td>
<td>Overall cytotoxicity (decreased in frail elderly), CD16-mediated cytotoxicity</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Solana et al., Immunity, 2006*
Aging and T Cell Homeostasis

Age-dependent decline in thymic output

Box 2. The immune risk phenotype (IRP)

Longitudinal studies are beginning to show that an ‘immune risk phenotype’ can be determined in the very old. Importantly, this seems independent of current clinical health status.

Parameters included in the IRP

* CD4:CD8 ratio of <1
* Poor T-cell proliferative responses to mitogens
* Increased CD8^+, CD28^−, CD57^+ cells
* Low B cells
* Cytomegalovirus (CMV)-seropositivity

As hypothesized here:

* Clonal expansions of CD8 cells carrying receptors for CMV or Epstein–Barr virus (EBV) antigens
* A high proportion of dysfunctional cells among the CMV-specific CD8 cells, which are CD28^− but positive for a natural-killer (NK)^− receptor, killer cell lectin-like receptor G1 (KLRG-1), cannot proliferate, secrete little interferon-γ (IFN-γ) but retain interleukin-10 (IL-10) secretion capacity.

Note that the IRP consists of a cluster of these parameters, not each parameter individually. Which are the most important and which additional factors are involved remains to be determined.
RELATIONSHIP BETWEEN IMMUNE PARAMETERS AND MORTALITY

CD4/CD8 > 1

CD4/CD8 < 1

CMV+

Wikby et al. 2006
Result: an accumulation of dysfunctional cells

Conclusion: In IRP elderly, dysfunctional CD8+ CMV-specific T cells accumulate because apoptotic pathways are compromised.

Hypothesis: Because T cell homeostasis maintains constant numbers of T cells in the periphery, even if naive cells continue to be generated from the thymus, the T cell repertoire will be shrunken, contributing to increased susceptibility to infectious disease.
Human immunosenescence: is it infectious?

Summary: Morbidity and mortality due to infectious disease is greater in the elderly than in the young, at least partly because of age-associated decreased immune competence, which renders individuals more susceptible to pathogens. This susceptibility is particularly evident for novel infectious agents such as in severe acute respiratory syndrome but is also all too apparent for common pathogens such as influenza. Many years ago, it was noted that the elderly possessed oligoclonal expansions of \( T \) cells, especially of \( CD8^+ \) cells. At the same time, it was established that cytomegalovirus (CMV) seropositivity was associated with many of the same phenotypic and functional alterations to \( T \)-cell immunity that were being reported as biomarkers associated with aging. It was discovered that CMV was the prime driving force behind most of the oligoclonal expansions and altered phenotypes and functions of \( CD8^+ \) cells. Independently, longitudinal studies of a free-living population of the very old in Sweden over the past decade have led to the emerging concept of an 'immune risk phenotype' (IRF), predicting mortality, which was itself found to be associated with CMV seropositivity. These findings support our hypothesis that the manner in which CMV and the host immune system interact is critical in determining the IRF and hence is predictive of mortality. In this sense, then, we suggest that immunosenescence is contagious.
Many CMV-specific CD8 cells in the elderly show hallmarks of ANERGY:

- They respond to direct stimulation with PMA/Io but not to specific antigen.
- They are apoptosis-resistant.
- They express low levels of CD28.
CMV decreases in CD28 and CD27

Fig. 5. Decreased expression of CD28 and CD27 in cytomegalovirus (CMV)-specific CD8+ T cells from elderly individuals.

CD27 transduces signals involved in the activation of NF-KB
CD8+ in elderly

Fig. 3. Increased percentage of cytomegalovirus (CMV)-specific CD8+ in elderly individuals compared with young donors.
IMMUNOSENCENCE

NAIVE CELLS

MEMORY CELLS
B cells in the aged: CD27, CD5, and CD40 expression

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Abstract

Aging is characterized by numerous changes in lymphocyte subpopulations. In the present paper
we discuss the surface markers CD27, CD5 and CD40. CD27 is considered a marker of primed
memory B cells and promotes the differentiation of memory B cells into plasma cells. CD5 is expressed on B1 cells,
responsible for T-cell-independent antibody production other than autoantibodies. The CD40 molecule
is necessary for T-dependent antibody responses. Here we show that the absolute number of CD5+ and
CD27+ B lymphocytes only marginally decrease in centenarians. However, there is
an increase of CD27+ B cells, while CD40 does not change significantly. These data
suggest different regulation of antibody production in the elderly while
of immune remodeling with aging, based on interactions between human B and NK cells.

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A Study of Serum Immunoglobulin Levels in Elderly Persons That Produces New Insights into B Cell Immunosenescence

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‡Dipartimento di Patologia Sperimentale e Centro Interdipartimentale “L. Galvani,” Università di Bologna, Bologna, Italy, and Istituto Nazionale di Ricerca per lo Sviluppo e lo Studio delle Malattie Infettive, Palermo, Italy

ABSTRACT: The literature on immunosenescence has focused mainly on T cell impairment. With the aim of gaining insights into B cell immunosenescence, we investigated the serum immunoglobulin levels in a cohort of 106 subjects (20–106 years). Serum IgG, IgM, and IgG subclasses were quantified by the nephelometric technique, IgE by CAP system fluorescence enzyme immunoassay, and IgD by radial immunodiffusion (RID). There was an age-related increase of IgG and IgA; the IgG age-related increase was significantly in men, but IgG1 levels showed an age-related increase only in men, whereas IgG3 showed an age-related increase only in women. IgM levels remained unchanged, whereas IgD and IgM serum levels decreased with age; the IgM age-related decrease was significant only in women, likely due to the relatively small sample size of aged men. Thus, in the elderly, the B cell repertoire available to respond to new antigenic challenges decreased. A lot of memory IgD—B cells are filling immunological space and the amount of naive IgD—B cells is dramatically decreased. The shift away from a population of predominantly naive B cells likely reflects the influence of cumulative exposure to foreign pathogens over time. These age-dependent B cell changes indicate

TABLE 1. Age-related serum concentrations of immunoglobulins (mean and 95% CI)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>IgG mg/L</th>
<th>IgA mg/L</th>
<th>IgM mg/L</th>
<th>IgD IU/mL</th>
<th>IgE kU/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>21-43 yrs (n = 46)</td>
<td>9.780 (8.711–10.861)</td>
<td>1.888 (1.650–2.146)</td>
<td>1.407 (1.203–1.611)</td>
<td>21.7 (14.2–33.2)</td>
<td>226 (66.5–719)</td>
</tr>
<tr>
<td>66-96 yrs (n = 85)</td>
<td>10.688 (9.911–10.865)</td>
<td>3.211 (2.834–3.588)</td>
<td>1.079 (0.927–1.232)</td>
<td>7.3 (2.4–12.3)</td>
<td>189.5 (57.5–321.5)</td>
</tr>
<tr>
<td>99-108 yrs (n = 35)</td>
<td>13.045 (12.047–14.042)</td>
<td>4.739 (4.049–4.218)</td>
<td>1.011 (0.863–1.128)</td>
<td>3.2 (2.5–3.8)</td>
<td>172.1 (71.1–273.2)</td>
</tr>
</tbody>
</table>

Spacemen's rank significant correlation between age and serum immunoglobulin concentrations:

IgG = 0.0004; IgA < 0.0001; IgM = 0.0002; IgD < 0.0001.

TABLE 3. Age-related serum concentrations of IgG subclasses of (mean and 95% CI)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>IgG1 mg/L</th>
<th>IgG2 mg/L</th>
<th>IgG3 mg/L</th>
<th>IgG4 mg/L</th>
</tr>
</thead>
</table>

Spacemen's rank significant correlation between age and serum subclasses of IgG concentrations:

IgG1 = 0.0009; IgG2 = 0.0009; IgG3 = 0.0009; IgG4 = 0.0009.
B cells subsets: young versus old

NAIVE (IGD+CD27-)

\[ \rho = -0.26 \]

\[ p = 0.005 * \]

MEMORY UNSWITCHED (IGD+CD27+)

\[ \rho = +0.019 \]

\[ p = 0.9 \]

MEMORY SWITCHED (IGD-CD27+)

\[ \rho = +0.02 \]

\[ p = 0.7 \]

DOUBLE NEGATIVE (IGD-CD27-)

\[ \rho = +0.46 \]

\[ p = 0.0001 * \]
Immunosenescence is characterized by:

1) the shrinkage of the T cell repertoire and the accumulation of oligoclonal expansions of memory/effector cells directed toward ubiquitous infectious agents;

2) decrease of circulating B cells; impaired antigen-specific antibody response although the Ig levels are not impaired.

3) chronic inflammatory status.
Immunological Markers

- No immune risk phenotype (IRP)
  - Maintained CD4:CD8 ratio
  - Preserved lymphoproliferative response
- Antigen presentation conserved
  - Decreased number of APC
  - Increased functional capacity
- NK cytotoxicity well preserved
  - Increased number of NK cells
  - Decreased per-cell cytotoxicity

HEALTH AND SURVIVAL

- Immune risk phenotype (IRP)
  - Diminished CD4:CD8 ratio
  - High numbers of CD8+CD28null
  - Low lymphoproliferative response
  - Very restricted CD8 T cell repertoire
  - CMV seropositivity
- Antigen presentation decreased
  - Low expression of costimulatory molecules
  - Low production of IL12
  - NK-mediated cytotoxicity diminished

MORBIDITY AND MORTALITY

Fig. 1 Immunological biomarkers of ageing in man: changes in both innate and adaptive immunity are associated with health and longevity. The “immune risk phenotype” (IRP) constitutes a major predictor of non-survival in longitudinal studies in octogenarians and nonagenarians. Whereas the T cell parameters included in the IRP are not so susceptible to variations in the clinical state and health of the donors, other immunological criteria are affected by age-associated morbidity. Thus overall NK cell cytotoxicity and antigen presentation are well preserved in healthy ageing but substantially diminished in non-healthy and frail elderly.
Age-related diseases

ALZHEIMER’S DISEASE
Alzheimer's disease: amyloid deposition is the main pathogenetic mechanism. Accumulation of Aβ peptide may be caused by 1) gene mutations (PS1, PS2 and APP human mutations in mendelian form of Alzheimer's disease) 2) genotype (and/or phenotype) favouring imbalanced inflammatory responses (pro-inflammatory genotype/anti-inflammatory genotype).
Risk factors

Age
Gender
Genetics
ApoE4
Cholesterol
Head injury
Smoking
Inflammation

Protective factors

Estrogen (?)
Education
Anti-oxidants (?)
NSAIDs
In the Rotterdam study, a large prospective cohort study of people 55 years of age or older, risk reduction for AD due to NSAIDs was dependent on the cumulative duration of use. While short-term use (1 month) was not beneficial, use for 2 years or longer reduced risk by 80%.
Protective effects of NSAIDs on the development of Alzheimer disease
Steven C. Vlad, Donald R. Miller, Neil W. Kowall and David T. Felson
*Neurology* 2008;70:1672-1677
DOI: 10.1212/01.wnl.0000311269.57716.63

**Background:** Nonsteroidal anti-inflammatory drugs (NSAIDs) may protect against Alzheimer disease (AD), but observational studies and trials have offered contradictory results. Prior studies have also been relatively short and small. We examined the effects on AD risk of NSAID use for >5 years and of NSAIDs that suppress formation of Aβ_{42} amyloid in a large healthcare database.

**Methods:** Cases were veterans aged 55 years and older with incident AD using the US Veterans Affairs Health Care system. Matched controls were drawn from the same population. NSAID exposure was categorized into seven time periods: none, ≤1 year, >1 but ≤2 years, and so on. Using conditional logistic regression, adjusted for race and comorbidities, we tested the association between AD development and the use of 1) any NSAID, 2) any NSAID excluding nonacetylated salicylates, 3) each NSAID class, 4) each individual NSAID, and 5) Aβ_{42}-suppressing NSAIDs.

**Results:** We identified 49,349 cases and 196,850 controls. Compared with no NSAID use, the adjusted odds ratios for AD among NSAID users decreased from 0.98 for ≤1 year of use (95% CI 0.95-1.00) to 0.76 for >5 years of use (0.68-0.85). For users of ibuprofen, it decreased from 1.03 (1.00-1.06) to 0.96 (0.92-0.99). Effects of other NSAID classes and individual NSAIDs were inconsistent. There was no difference between a group of Aβ_{42}-suppressing NSAIDs and others.

**Discussion:** Long-term nonsteroidal anti-inflammatory drug (NSAID) use was protective against Alzheimer disease. Findings were clearest for ibuprofen. Aβ_{42}-suppressing NSAIDs did not differ from others. *Neurology* 2008;70:1672-1677
### Infiammation and Dementia
A 25-Year Follow-up of the Honolulu-Asia Aging Study

#### Table 2. Crude Relationship between Midlife High-Sensitivity C-Reactive Protein Levels and Late-Life Dementia: The Honolulu-Asia Aging Study

<table>
<thead>
<tr>
<th>Quartiles of hs-CRP</th>
<th>All Dementia (n = 214), OR (CI)</th>
<th>AD (n = 95), OR (CI)</th>
<th>AD w/CVD (n = 36), OR (CI)</th>
<th>VaD (n = 73), OR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (&lt;0.34 mg/L)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>2 (0.34–0.56 mg/L)</td>
<td>2.9 (1.7–5.0)</td>
<td>2.6 (1.2–5.5)</td>
<td>3.6 (1.0–13.1)</td>
<td>3.5 (1.3–9.8)</td>
</tr>
<tr>
<td>3 (0.57–1.00 mg/L)</td>
<td>3.8 (2.2–6.6)</td>
<td>3.9 (1.9–8.0)</td>
<td>3.2 (0.8–12.3)</td>
<td>5.2 (1.9–14.1)</td>
</tr>
<tr>
<td>4 (&gt;1.00 mg/L)</td>
<td>2.7 (1.6–4.7)</td>
<td>1.6 (0.7–3.6)</td>
<td>4.2 (1.5–15.0)</td>
<td>5.7 (1.1–12.0)</td>
</tr>
<tr>
<td>p trend</td>
<td>&lt;0.0005</td>
<td>&lt;0.14</td>
<td>&lt;0.05</td>
<td>&lt;0.002</td>
</tr>
</tbody>
</table>

*Compared with nondemented (n = 836): odds ratio compares risk with first quartile, adjusted for age.

AD = Alzheimer’s disease with no contributing cerebrovascular disease; AD w/CVD = AD with associated cerebrovascular disease; CI = confidence interval; hs-CRP = high-sensitivity C-reactive protein; OR = odds ratio; VaD = vascular dementia.
Alzheimer’s Disease and Peripheral Infections: The Possible Contribution from Periodontal Infections, Model and Hypothesis


Fig. 2. Model for PD-induced progression of AD. The central theme of AD pathogenesis is the inflammation as illustrated by the activated glial cell that produces high levels of inflammatory molecules such as IL-1β, IL-6, TNF-α and CRP. PD may affect the initiation, progression of AD by directly (bacterial invasion) or indirectly (LPS, cytokines, CRP) increase brain inflammation via neuronal or systemic pathways. These molecules would further amplify the inflammatory signal by activating the already primed glial cells and increase production of molecules such as Aβ peptide, hyperphosphorylated tau proteins and ultimately activate pathways leading to degeneration.
Table 1
Markers of inflammation in the brain of patients with neuropathological diagnosis of AD

<table>
<thead>
<tr>
<th>Acute phase proteins</th>
<th>Classical complement proteins</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-1-Antichymotrypsin</td>
<td>Clq</td>
</tr>
<tr>
<td>α-1-Antitrypsin</td>
<td>C4</td>
</tr>
<tr>
<td>α-2-Macroglobulin</td>
<td>C4d</td>
</tr>
<tr>
<td>C-Reactive protein</td>
<td>C3</td>
</tr>
<tr>
<td>Serum amyloid substance P</td>
<td>C3b, C3c, C3d</td>
</tr>
<tr>
<td>Amyloid precursor protein</td>
<td>C7, C9, C5, C9 (MAC)</td>
</tr>
<tr>
<td>Complement defense proteins</td>
<td>Complement receptors</td>
</tr>
<tr>
<td>MIRL</td>
<td>CR3</td>
</tr>
<tr>
<td>Clusterin (APOJ)</td>
<td>CR4</td>
</tr>
<tr>
<td>Vibriococin</td>
<td></td>
</tr>
<tr>
<td>C4BP</td>
<td></td>
</tr>
<tr>
<td>C1-inhibitor</td>
<td></td>
</tr>
<tr>
<td>Cytokines</td>
<td>Cytokine receptors</td>
</tr>
<tr>
<td>IL-1α and IL-1β</td>
<td>IL-2R</td>
</tr>
<tr>
<td>IL-6</td>
<td></td>
</tr>
<tr>
<td>TNF</td>
<td></td>
</tr>
<tr>
<td>TGFβ1</td>
<td></td>
</tr>
<tr>
<td>S100β</td>
<td></td>
</tr>
<tr>
<td>Histocompatibility molecules</td>
<td></td>
</tr>
<tr>
<td>MHC I</td>
<td></td>
</tr>
<tr>
<td>MHC II, HLA-DR, DQ, DP</td>
<td></td>
</tr>
<tr>
<td>Leukocyte antigens</td>
<td>Leucocyte adhesion molecules</td>
</tr>
<tr>
<td>CD45</td>
<td>ICAM-1</td>
</tr>
<tr>
<td>Reactive gliosis and microglia activation</td>
<td></td>
</tr>
</tbody>
</table>
Activated microglia, expressing major histocompatibility complex type II (MHC II) (brown), infiltrating a classical senile plaque (immunostained for A, black). There are also increased numbers of activated microglia in surrounding neuropil. Scale bar: 50 m.
INFLAMMATORY molecules IN THE AD SENILE PLAQUE

Neuritic plaque

COX-2

β-A4

ApoE

β-APP

TGF-β1, β-FGF
NGF, PMA

α1-ACT

IL-10

TLR4

5-LO

COX-2

Neuronal death

IL-10

NO²⁻

IL-10

Blood vessel

S100β

Astrocyte

Up-regulation

Activation

Polymerisation
### Table 1 – List of studies concerning AD and inflammatory gene polymorphisms

<table>
<thead>
<tr>
<th>Gene</th>
<th>Polymorphisms</th>
<th>Type of study</th>
<th>AD association</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLR4</td>
<td>Asp299Gly</td>
<td>Case-control</td>
<td>Pos</td>
<td>Minoretti et al., 2006</td>
</tr>
<tr>
<td>COX-2</td>
<td>Rs20417</td>
<td>Case-control</td>
<td>Pos</td>
<td>Abdullah et al., 2006</td>
</tr>
<tr>
<td>COX-2</td>
<td>Rs689466</td>
<td>Case-control</td>
<td>Neg</td>
<td>Reiman et al., 2007</td>
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<tr>
<td>COX-2</td>
<td>Rs689466</td>
<td>Case-control</td>
<td>Pos</td>
<td>Ma et al., 2007</td>
</tr>
<tr>
<td>5-LOX</td>
<td>GGcGGG</td>
<td>Case-control</td>
<td>Pos</td>
<td>Qu et al., 2001</td>
</tr>
<tr>
<td>5-LOX</td>
<td>Various SNPs</td>
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<td>Neg</td>
<td>Morgan et al., 2007</td>
</tr>
<tr>
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<td>−889</td>
<td>Meta-analysis</td>
<td>Pos</td>
<td>Rainero et al., 2004</td>
</tr>
<tr>
<td>IL-1β</td>
<td>−511</td>
<td>Meta-analysis</td>
<td>Pos</td>
<td>Di Bona et al. Ms to be submitted</td>
</tr>
<tr>
<td>IL-1β</td>
<td>+3953</td>
<td>Meta-analysis</td>
<td>Pos</td>
<td>Di Bona et al. Ms to be submitted</td>
</tr>
<tr>
<td>IL-6</td>
<td>−174</td>
<td>Meta-analysis</td>
<td>Neg</td>
<td>Di Bona et al. Ms to be submitted</td>
</tr>
<tr>
<td>IL-10</td>
<td>−1082</td>
<td>Meta-analysis</td>
<td>Pos</td>
<td>Di Bona et al. Ms to be submitted</td>
</tr>
</tbody>
</table>

In the positive studies the pro-inflammatory alleles of LPS co-receptors TLR4, the enzymes involved in prostaglandins (COX-2) and leukotrienes (5-LOX) synthesis, the pro-inflammatory cytokines IL-1α, IL-1β and the anti-inflammatory cytokine IL-10 were significantly increased in AD patients.

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**Review**

**Inflammation, genes and zinc in Alzheimer’s disease**

Sonya Vasto\(^a\), Giuseppina Candore\(^a\), Florinda Listi\(^a\), Carmela Rita Balistreri\(^a\), Giuseppina Colonna-Romano\(^a\), Marco Malavolta\(^b\), Domenico Lio\(^b\), Domenico Nuzzo\(^c,d\), Eugenio Macchegiani\(^b\), Danilo Di Bona\(^e,e\), Calogero Caruso\(^e,e\).

\(^a\)Department of Pathology and Biomedical Methodology, University of Palermo, Corso Tukory, 211, 90134 Palermo, Italy
\(^b\)Immunology Research Department, INRCA, Ancona, Italy
\(^c\)Institute of Biomathematics and Molecular Immunology, National Research Council, Palermo, Italy
**Review**

**Association between the interleukin-1β polymorphisms and Alzheimer's disease: A systematic review and meta-analysis**

Danilo Di Bona a, b, c, Antonella Plaia a, Sonya Vasto a, c, Luca Cavallone a, Francesco Lecce a, Claudio Franceschini a, Federico Licastro b, Giuseppe Colonna-Romano a, Domenico Lio c, Giuseppina Candore a, Calogero Caruso b, c, *

---

**Table:**

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>TT n/N</th>
<th>CC+CT n/N</th>
<th>OR (random)</th>
<th>Weight %</th>
<th>OR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>01 Caucasian</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grimaldi</td>
<td>46/91</td>
<td>271/541</td>
<td>7.01</td>
<td>1.31</td>
<td>[0.82, 2.10]</td>
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<tr>
<td>Minster</td>
<td>40/59</td>
<td>296/479</td>
<td>10.08</td>
<td>1.00</td>
<td>[0.53, 2.05]</td>
</tr>
<tr>
<td>Green</td>
<td>57/66</td>
<td>245/679</td>
<td>10.08</td>
<td>1.00</td>
<td>[0.53, 2.05]</td>
</tr>
<tr>
<td>Herley</td>
<td>20/67</td>
<td>190/504</td>
<td>7.10</td>
<td>1.34</td>
<td>[0.80, 2.24]</td>
</tr>
<tr>
<td>Ehi</td>
<td>11/29</td>
<td>100/268</td>
<td>2.65</td>
<td>0.26</td>
<td>[0.15, 0.89]</td>
</tr>
<tr>
<td>Mattila</td>
<td>10/29</td>
<td>82/138</td>
<td>4.22</td>
<td>0.94</td>
<td>[0.47, 1.87]</td>
</tr>
<tr>
<td>Bosco</td>
<td>19/37</td>
<td>133/281</td>
<td>3.00</td>
<td>0.69</td>
<td>[0.33, 1.13]</td>
</tr>
<tr>
<td>McCulley</td>
<td>5/24</td>
<td>124/266</td>
<td>5.46</td>
<td>0.92</td>
<td>[0.42, 1.56]</td>
</tr>
<tr>
<td>Seripa Italy</td>
<td>25/44</td>
<td>200/324</td>
<td>3.63</td>
<td>0.34</td>
<td>[0.24, 1.29]</td>
</tr>
<tr>
<td>Seripa USA</td>
<td>11/25</td>
<td>91/219</td>
<td>3.58</td>
<td>0.76</td>
<td>[0.32, 1.79]</td>
</tr>
<tr>
<td>Yeha</td>
<td>9/26</td>
<td>91/219</td>
<td>2.96</td>
<td>0.76</td>
<td>[0.42, 1.56]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>507</td>
<td>3812</td>
<td>17.96</td>
<td>0.98</td>
<td>[0.77, 1.23]</td>
</tr>
</tbody>
</table>

**Total events: 247 (TT), 1846 (CC+CT)**

Test for heterogeneity: $Q^p = 14.29, df = 10 (P = 0.16), I^2 = 30.0\%$

Test for overall effect: $Z = 0.21 (P = 0.83)$

**C2 Non-Caucasian**

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>TT n/N</th>
<th>CC+CT n/N</th>
<th>OR (random)</th>
<th>Weight %</th>
<th>OR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu</td>
<td>24/78</td>
<td>111/249</td>
<td>7.12</td>
<td>0.98</td>
<td>[0.67, 1.59]</td>
</tr>
<tr>
<td>Ma</td>
<td>38/83</td>
<td>92/107</td>
<td>6.22</td>
<td>0.69</td>
<td>[0.52, 1.59]</td>
</tr>
<tr>
<td>Nishimura</td>
<td>34/71</td>
<td>190/264</td>
<td>6.94</td>
<td>0.68</td>
<td>[0.52, 1.59]</td>
</tr>
<tr>
<td>Wang 1</td>
<td>16/40</td>
<td>20/109</td>
<td>4.44</td>
<td>0.76</td>
<td>[0.25, 1.56]</td>
</tr>
<tr>
<td>Wang 2</td>
<td>38/86</td>
<td>101/342</td>
<td>7.79</td>
<td>1.00</td>
<td>[0.44, 1.33]</td>
</tr>
<tr>
<td>Younchik</td>
<td>25/167</td>
<td>212/74</td>
<td>7.10</td>
<td>1.09</td>
<td>[0.15, 1.56]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>507</td>
<td>3812</td>
<td>17.96</td>
<td>0.98</td>
<td>[0.77, 1.23]</td>
</tr>
</tbody>
</table>

**Total events: 223 (TT), 724 (CC+CT)**

Test for heterogeneity: $Q^p = 11.17, df = 5 (P = 0.05), I^2 = 65.2\%$

Test for overall effect: $Z = 0.32 (P = 0.75)$

**Total (95% CI)**

| Total events: 470 (TT), 2589 (CC+CT) | 1012 | 5597 | 160.00 | 1.01 | [0.84, 1.21] |

Test for heterogeneity: $Q^p = 25.54, df = 16 (P = 0.08), I^2 = 37.9\%$

Test for overall effect: $Z = 0.86 (P = 0.35)$

---

**Figure 2:** Meta-analysis of 17 case-control studies (11 Caucasian and 6 non-Caucasian) of the IL-1β-511 polymorphism and the risk for AD using the random effects model. The odds ratio (OD) and 95% confidence interval (CI) for the effect of the TT genotype for the risk of AD are plotted on the graph. Studies are arranged chronologically based on the year of publication.
**Fig. 1** - Meta-analysis of 5 case-control studies of the IL-1β +3953 polymorphism and the risk for AD using the random effects model. The odds ratio (OD) and 95% confidence interval (C.I.) for the effect of the TT genotype for the risk of AD are plotted on the graph. Studies are arranged chronologically based on the year of publication.

<table>
<thead>
<tr>
<th>Study</th>
<th>TT</th>
<th>CC+CT</th>
<th>OR (random)</th>
<th>Weight</th>
<th>OR (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicoll</td>
<td>17/25</td>
<td>215/274</td>
<td>14.27</td>
<td>1.67 [0.66, 2.79]</td>
<td></td>
</tr>
<tr>
<td>Hedley</td>
<td>19/39</td>
<td>202/629</td>
<td>21.06</td>
<td>2.26 [1.11, 4.61]</td>
<td></td>
</tr>
<tr>
<td>Sniecka</td>
<td>35/69</td>
<td>210/566</td>
<td>42.96</td>
<td>1.45 [0.89, 2.30]</td>
<td></td>
</tr>
<tr>
<td>Rosenmann</td>
<td>9/18</td>
<td>99/194</td>
<td>11.44</td>
<td>0.96 [0.37, 2.52]</td>
<td></td>
</tr>
<tr>
<td>Veitl</td>
<td>9/15</td>
<td>88/222</td>
<td>9.37</td>
<td>2.28 [0.75, 6.64]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td>100.00</td>
<td>1.60 [1.16, 2.22]</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2 = 5.27$, df = 4 ($p = 0.33$), $I^2 = 0$

Test for overall effect: $Z = 2.93$ ($p = 0.003$)

---

**Fig. 3** - Meta-analysis (using a random effects model) of the four Caucasian case-control studies, with a statistical power > 0.18, of the IL-1β -511 polymorphism and the risk for AD. The odds ratio (OD) and 95% confidence interval (C.I.) for the effect of the TT genotype for the risk of AD are plotted on the graph. Studies are arranged chronologically based on the year of publication.

<table>
<thead>
<tr>
<th>Study</th>
<th>TT</th>
<th>CC+CT</th>
<th>OR (random)</th>
<th>Weight</th>
<th>OR (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grimaldi</td>
<td>45/81</td>
<td>271/541</td>
<td>27.94</td>
<td>1.21 [0.80, 1.60]</td>
<td></td>
</tr>
<tr>
<td>Minster</td>
<td>49/59</td>
<td>295/479</td>
<td>18.63</td>
<td>1.31 [0.74, 2.34]</td>
<td></td>
</tr>
<tr>
<td>Green</td>
<td>37/86</td>
<td>249/679</td>
<td>29.98</td>
<td>1.30 [0.83, 2.06]</td>
<td></td>
</tr>
<tr>
<td>Hedley</td>
<td>30/67</td>
<td>190/504</td>
<td>23.43</td>
<td>1.84 [0.80, 2.64]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td>100.00</td>
<td>1.22 [1.05, 1.69]</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2 = 0.01$, df = 3 ($p = 1.00$), $I^2 = 0$

Test for overall effect: $Z = 2.16$ ($p = 0.03$)
**Review**

**Systematic review by meta-analyses on the possible role of TNF-α polymorphisms in association with Alzheimer’s disease**

Danilo Di Bona\(^a,b\), Giuseppina Candore\(^a\), Claudio Franceschi\(^c\), Federico Licastro\(^c\), Giuseppina Colonna-Romano\(^a\), Calogero Cammà\(^d\), Domenico Lio\(^a\), Calogero Caruso\(^a,b,\ast\)

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**Fig. 1** – Meta-analysis of 11 case-control studies of the TNF-α −308 polymorphism and the risk for AD using the random-effects model. The odds ratio (OR) and 95% confidence interval (CI) for the effect of AA genotype for the risk of AD are plotted on the graph. Studies are arranged chronologically based on the year of publication.
Role of Cyclooxygenase-2 and 5-Lipoxygenase Polymorphisms in Alzheimer’s Disease in a Population from Northern Italy: Implications for Pharmacogenomics

Florinda Listi³, Calogero Caruso³, Domenico Lio³, Giuseppina Colonna-Romano³, Martina Chiappelli³, Federico Licastro³, Giuseppina Candore³

<table>
<thead>
<tr>
<th>Locus/Codon</th>
<th>Genotype/allele</th>
<th>AD (n=341)</th>
<th>Control (n=590)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>-765 G/C (COX-2)</td>
<td>GG</td>
<td>237 (69.5%)</td>
<td>115 (60.5%)</td>
<td>0.032*</td>
</tr>
<tr>
<td></td>
<td>GC</td>
<td>94 (27.5%)</td>
<td>62 (32.6%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CC</td>
<td>10 (3%)</td>
<td>13 (6.9%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>G</td>
<td>568 (33.3%)</td>
<td>297 (73.2%)</td>
<td>0.037**</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>114 (6.7%)</td>
<td>82 (21.2%)</td>
<td></td>
</tr>
<tr>
<td>-1766 G/A (5-LOX)</td>
<td>GG</td>
<td>258 (75.9%)</td>
<td>150 (81.1%)</td>
<td>0.018*</td>
</tr>
<tr>
<td></td>
<td>GA</td>
<td>77 (22.2%)</td>
<td>31 (16.3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AA</td>
<td>8 (2.5%)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>G</td>
<td>529 (86.4%)</td>
<td>369 (91.3%)</td>
<td>0.007**</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>93 (13.6%)</td>
<td>31 (8.7%)</td>
<td></td>
</tr>
<tr>
<td>-1761 G/A (5-LOX)</td>
<td>GG</td>
<td>223 (65.4%)</td>
<td>137 (78.2%)</td>
<td>0.012*</td>
</tr>
<tr>
<td></td>
<td>GA</td>
<td>112 (32.2%)</td>
<td>53 (28.9%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AA</td>
<td>6 (1.8%)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>G</td>
<td>552 (98.2%)</td>
<td>327 (96.6%)</td>
<td>0.007**</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>124 (18%)</td>
<td>53 (14.4%)</td>
<td></td>
</tr>
<tr>
<td>-325 G/A (PLAP)</td>
<td>GG</td>
<td>272 (80%)</td>
<td>146 (74.8%)</td>
<td>0.061*</td>
</tr>
<tr>
<td></td>
<td>GA</td>
<td>62 (18%)</td>
<td>44 (21.3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AA</td>
<td>7 (2%)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>G</td>
<td>606 (88.8%)</td>
<td>336 (82.4%)</td>
<td>0.008**</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>76 (11.2%)</td>
<td>64 (11.6%)</td>
<td></td>
</tr>
</tbody>
</table>

The significance of the different genotype distribution between patients and controls was calculated by chi-square test (2x2 table). The significance of the different allele distribution between patients and controls was calculated by chi-square test (1x2 table).


![Diagram showing lipid peroxidation and inflammation pathways]
Systemic infections and inflammation affect chronic neurodegeneration

V. Hugh Perry, Colin Cunningham and Clive Holmes

Abstract | It is well known that systemic infections cause flare-ups of disease in individuals with asthma and rheumatoid arthritis, and that relapses in multiple sclerosis can often be associated with upper respiratory tract infections. Here we review evidence to support our hypothesis that in chronic neurodegenerative diseases such as Alzheimer’s disease, with an ongoing innate immune response in the brain, systemic infections and inflammation can cause acute exacerbations of symptoms and drive the progression of neurodegeneration.


Association between dementia and infectious disease: evidence from a case-control study.

Dunn N, Mullee M, Perry VH, Holmes C.

University of Southampton, UK. nick.dunn@soton.ac.uk

Inflammation plays a part in the etiology of dementia. Whether this is the primary pathogenesis, or a secondary reaction is unclear. We postulate that since systemic infection can provoke the enhanced synthesis of inflammatory mediators in the brain, such diseases may promote the onset of dementia. We carried out a nested case-control study using the General Practice Research Database. Cases were patients with incident dementia, and controls without such a diagnosis. Infections episodes in the four years preceding diagnosis were counted using diagnostic codes, or prescription codes for anti-infective drugs. We considered age, sex, smoking, diabetes mellitus, and frequency of consultation as potential confounders. There were 9954 valid cases, and 9374 valid controls. Cases were on average older, more likely to be female, to smoke and to have diabetes, than the controls. There was an increased risk of diagnosis of dementia in those patients older than 84 with infections (OR for 2 or more infections compared with 0 or 1 = 1.4, 95% CI 1.2 to 1.7). Smoking and diabetes mellitus were also shown to markedly increase the risk of diagnosis of dementia. We have shown a positive association between episodes of infection and increased likelihood of diagnosis of dementia in the elderly. Smoking and diabetes mellitus are associated with onset of dementia in the elderly. The evidence from this study may represent cause and effect, since there is a credible biologic explanation.
Association between the Polymorphisms of TLR4 and CD14 Genes and Alzheimer’s Disease

C.R. Balistreri¹, M.P. Grimaldi¹, M. Chiappelli¹², F. Licastro², L. Castiglia¹, F. Listi¹, S. Vasto¹, D. Lio¹, C. Caruso¹ and G. Candore¹,*

¹Immunosenescence Unit, Department of Pathobiology and Biomedical Methodologies, University of Palermo, Palermo, Italy and ²Department of Experimental Pathology, University of Bologna, Bologna, Italy

Table 1. Genotype Distributions and Allelic Frequencies of +896A/G(Asp299Gly) TLR4 Gene polymorphism in 626 AD Patients and 190 Controls from Northern Italy

<table>
<thead>
<tr>
<th>Genotypes</th>
<th>AD Patients (N=626)</th>
<th>Controls (N=190)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLR4A/A</td>
<td>569</td>
<td>161</td>
</tr>
<tr>
<td>A/G</td>
<td>54</td>
<td>28</td>
</tr>
<tr>
<td>G/G</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

Alleles  | AD Patients (N=626) | Controls (N=190) |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TLR4 +896A</td>
<td>1192 (95.2%)</td>
<td>350 (92.1%)</td>
</tr>
<tr>
<td>+896G</td>
<td>60 (4.8%)</td>
<td>30 (7.9%)</td>
</tr>
</tbody>
</table>

All the genotypes were in Hardy-Weinberg equilibrium. Significant differences by χ² (3x2 table) in the frequency of +896A/G TLR4 SNP genotypes between the patients and controls were found (p=0.04). Significance was obtained by χ² (2x2 table) in allelic frequency of this SNP: in particular, +896G TLR4 low responder allele was underrepresented in AD patients and overrepresented in controls, while +896A proinflammatory allele was overexpressed in AD patients (p=0.02).
Major histocompatibility complex and sporadic Alzheimer’s disease: a critical reappraisal

Giuseppina Candore, Carmela Rita Balistreri, Giuseppina Colonna-Romano, Domenico Lio, Calogero Caruso*

Gruppo di Studio sull’Immunosenescenza, Dipartimento di Biopatologia e Metodologie Biomediche, Università di Palermo, Corso Tusculano 211, 90124 Palermo, Italy

Received 23 June 2003; received in revised form 16 October 2003; accepted 16 October 2003
Association Between the HLA-A2 Allele and Alzheimer Disease

FLORINDA LISTI,1 GIUSEPPINA CANDORE,1 CARMELA RITA BALISTRERI,1 MARIA PAOLA GRIMALDI,1 VALENTINA ORLANDO,1 SONYA VASTO,1 GIUSEPPINA COLONNA-ROMANO,1 DOMENICO LIO,1 FEDERICO LICASTRO,2 CLAUDIO FRANCESCHI,2,3 and CALOGERO CARUSO

TABLE 1. Genotype Frequency of HLA-A2 Allele in 460 Patients with Sporadic AD and 266 Controls in Northern Italy

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th></th>
<th>AD patients</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>A2+</td>
<td>101</td>
<td>0.38</td>
<td>211</td>
<td>0.46</td>
</tr>
<tr>
<td>A2−</td>
<td>165</td>
<td>0.62</td>
<td>249</td>
<td>0.54</td>
</tr>
</tbody>
</table>

p = 0.04618045.
REMINDER - REGISTER NOW FOR TOMORROW'S WEBINAR

Herpes Simplex and Alzheimer's—Time to Think Again?

It may not make your Top 10 list of probable Alzheimer's causes, but herpes simplex virus 1 (HSV1) is attracting attention from a growing number of international research groups as a possible trigger for the feared disorder. Recent work has tied the virus to AD biomarkers, and offered some epidemiological and genetic support for the long-proposed connection between HSV1 reactivation and AD risk. Do the new findings make a case for this hypothesis?

Log in Tomorrow Thursday, 24 February 2011, at 11:30 a.m. U.S. Eastern Time, for a Webinar on herpes simplex virus and AD. Ruth Itzhaki, University of Manchester, U.K.; Elisa Porcellini, University of Bologna, Italy; Luc Letenneur, INSERM, Bordeaux, France; and Richard Stemmler, St. Jude Children's Research Hospital, Memphis, Tennessee, will share some of their latest research and field audience questions. Paul Kipper, herpes virologist at Manchester Royal Infirmary, U.K., and Terrence Town, Cedars-Sinai Medical Center, Los Angeles, will be on hand for discussion afterward.

Register for the Webinar by following the instructions provided.

Contact Us. Please send us technical questions prior to the actual event. (Select "Live Discussions Login/Technical Help" in the dropdown menu on the Contact Us form.)

Porcellini et al. Immunity & Ageing 2010, 7:16
http://www.immunityageing.com/content/7/1/16

HYPOTHESIS

Alzheimer's disease gene signature says: beware of brain viral infections

Elisa Porcellini, Ilaria Carbone, Manuela Ianni, Federico Licastro
We found combinations of alleles in eight inflammatory genes and ApoE that distinguish Alzheimer disease risk groups.
Sharing Pathogenetic Mechanisms between Acute Myocardial Infarction and Alzheimer’s Disease as Shown by Partially Overlapping of Gene Variant Profiles

Sonya Vasto¹, Martina Chiappelli¹, Claudio Marcello Caldarera², Elisa Porcellini¹, Ilaria Carbone¹, Calogero Caruso³, Domenico Lio³, Elizabeth H. Corder⁴

We investigated a panel of relevant polymorphisms to distinguish genetic backgrounds for AMI and AD: IL10 −1082G/A, IL6 −174G/C, TNF −308G/A, IFNG +874T/A, SERPINA3 −51G/T, HMGCR −911C/A, APOE ε2/3/4 (280 AMI cases, 257 AD cases, and 1307 population controls).

We conclude that AMI and AD share genetic backgrounds involving cholesterol metabolism and the up-regulation of inflammation and that gene-gene interactions in relevant sets of genes may be useful in defining inherited risk for common disorders.
Studies in animal models for AD support the notion that immune cells infiltrate the brain and may modulate the disease.

Britschgi & Wyss-Coray (2007)
The immune system

INNATE
- phagocytes
- dendritic cells
- NK cells
- Inflammation

INSTRUCTIVE
- B cells (humoral via antibodies)
- T cells (cellular effectors; cytokines)
- antigen-presenting cells
Inflammation, Cytokines, Immune Response, Apolipoprotein E, Cholesterol, and Oxidative Stress in Alzheimer Disease: Therapeutic Implications

Giuseppina Candore, Matteo Bulati, Calogero Caruso, Laura Castiglia, Giuseppina Colonna-Romano, Danilo Di Bona, Giovanni Duro, Domenico Lio, Domenica Matranga, Mariavaleria Pellicanò, Claudia Rizzo, Giovanni Scapagnini, and Sonya Vasto

Systemic Immune Responses in Alzheimer’s Disease: In Vitro Mononuclear Cell Activation and Cytokine Production

Mariavaleria Pellicanò, Matteo Bulati, Silvio Buffa, Mario Barbagallo, Anna Di Prima, Gabriella Misiano, Pasquale Picone, Marta Di Carlo, Domenico Nuzzo, Giuseppina Candore, Sonya Vasto, Domenico Lio, Calogero Caruso, and Giuseppina Colonna-Romano

*Gruppo di Studio sull’Immunosenescenza, Dipartimento di Biopatologia e Biotecnologie Mediche e Forensi, Università di Palermo, Italy
b Dipartimento di Medicina Clinica e delle Patologie Emergenti, Università di Palermo, Italy
Istituto di Biomedicina e Immunologia Molecolare, CNR, Palermo, Italy
Decrease amount of B cells in AD

Table 1

Lymphocyte subpopulations in 40 AD subjects and 25 HC. Data are expressed as Mean ± SD of the percentage and as absolute number.

<table>
<thead>
<tr>
<th>Subpopulations</th>
<th>HC % (Mean ± SD)</th>
<th>HC (Absolute number/μL)</th>
<th>AD % (Mean ± SD)</th>
<th>AD (Absolute number/μL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD3^+</td>
<td>67.3 ± 11.8</td>
<td>1196 ± 444</td>
<td>68.4 ± 9.2</td>
<td>1260 ± 420</td>
</tr>
<tr>
<td>CD4^+</td>
<td>44.3 ± 9.6</td>
<td>801 ± 310</td>
<td>45.7 ± 8.9</td>
<td>845.6 ± 340</td>
</tr>
<tr>
<td>CD8^+</td>
<td>20.0 ± 10.5</td>
<td>373 ± 214</td>
<td>21.0 ± 8.9</td>
<td>361 ± 160</td>
</tr>
<tr>
<td>CD19^+</td>
<td>9.8 ± 5.3</td>
<td>184 ± 128</td>
<td>7.0 ± 3.7*</td>
<td>110 ± 54*</td>
</tr>
<tr>
<td>CD3^-CD16^-γδ^+</td>
<td>17.2 ± 9</td>
<td>350 ± 195</td>
<td>15.7 ± 6.7</td>
<td>319 ± 165</td>
</tr>
<tr>
<td>CD3^-CD16^-γδ^+</td>
<td>3.0 ± 3.3</td>
<td>45 ± 55</td>
<td>2.5 ± 1.8</td>
<td>54 ± 39</td>
</tr>
</tbody>
</table>

Significance has been evaluated by ANOVA test. AD vs. HC *p = 0.01.
Fig. 2. Percentage (Mean ± SEM) of expression of early activation markers CD25 and CD69 on cells of HC (n = 13) and AD subjects (n = 18) cultured in medium (white) or with rAβ42 (black) for 48 h. Statistical analysis was performed by ANOVA test. Significant values are indicated.

Fig. 3. MFI (Mean ± SEM) of expression of CD36 (panel A) and CD80 and HLA-DR (panel B) on monocytes (CD14+) of HC (n = 15) and AD (n = 18) subjects cultured in medium (white) or with rAβ42 (black). Statistical analysis was performed by ANOVA test. Significant values are indicated.
Fig. 4. MFI (Mean ± SEM) expression of CCR2 and CCR5 on CD19+ cells from AD obtained from 15 HC subjects and 18 AD patients and cultured for 48 hours. (a) CCR2 expression on CD19+ cells from AD patients. (b) CCR5 expression on CD19+ cells from AD patients. (c) CCR2 expression on CD3+ cells from AD patients. (d) CCR5 expression on CD3+ cells from AD patients.

Table 2

<table>
<thead>
<tr>
<th>Cytokines</th>
<th>rAβ1-42 HC vs medium HC Increase (%) (median and p-25-p75 values)</th>
<th>rAβ1-42 AD vs medium AD Increase (%) (median and p-25-p75 values)</th>
<th>p1</th>
<th>p2</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1β</td>
<td>4 (0-25)</td>
<td>211 (133-285)</td>
<td>n.s.</td>
<td>0.01</td>
</tr>
<tr>
<td>IL-1α</td>
<td>66 (0-258)</td>
<td>202 (152-288)</td>
<td>n.s.</td>
<td>0.06</td>
</tr>
<tr>
<td>IL-6</td>
<td>0 (0-151)</td>
<td>410 (280-532)</td>
<td>n.s.</td>
<td>0.01</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>0 (0-52)</td>
<td>106 (84-134)</td>
<td>n.s.</td>
<td>0.02</td>
</tr>
<tr>
<td>TNF-α</td>
<td>0 (0-168)</td>
<td>63 (35-104)</td>
<td>n.s.</td>
<td>0.02</td>
</tr>
<tr>
<td>IL-10</td>
<td>0 (0-0)</td>
<td>236 (100-542)</td>
<td>n.s.</td>
<td>0.03</td>
</tr>
<tr>
<td>Growth Factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GM-CSF</td>
<td>0 (0-90)</td>
<td>77 (62-100)</td>
<td>n.s.</td>
<td>0.03</td>
</tr>
<tr>
<td>VEGF</td>
<td>0 (0-322)</td>
<td>32 (10-82)</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>PDGF bb</td>
<td>57 (0-283)</td>
<td>14 (0-26)</td>
<td>n.s.</td>
<td>0.01</td>
</tr>
<tr>
<td>G-CSF</td>
<td>0 (0-280)</td>
<td>547 (367-1367)</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Chemokines</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eotaxin</td>
<td>0 (0-128)</td>
<td>114 (98-141)</td>
<td>n.s.</td>
<td>0.03</td>
</tr>
<tr>
<td>MIP-1α</td>
<td>188 (0-577)</td>
<td>1710 (163-5032)</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>MIP-1β</td>
<td>74 (0-377)</td>
<td>465 (152-639)</td>
<td>n.s.</td>
<td>0.02</td>
</tr>
<tr>
<td>RANTES</td>
<td>275 (0-955)</td>
<td>123 (57-206)</td>
<td>n.s.</td>
<td>0.05</td>
</tr>
<tr>
<td>MCP-1(MCAF)</td>
<td></td>
<td></td>
<td></td>
<td>n.s.</td>
</tr>
</tbody>
</table>

p1 = Significance of differences between Medium and rAβ1-42 of HC; p2 = Significance of differences between Medium and rAβ1-42 of AD.
Biomarkers of aging

Sonya Vasto, Giovanni Scapagnini, Matteo Bulati, Giuseppina Candore, Laura Castiglia, Giuseppina Colonna-Romano, Domenico Lio, Domenico Nuzzo, Mariavaleria Pellicano, Claudia Rizzo, Nicola Ferrara, Calogero Caruso

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Take home message

• Involvement of systemic immunity in AD patients and old people.
• Events contributing to the onset and development of AD are numerous and complex.
• Hot topics involved in AD pathophysiology, such as inflammation, cytokines, immune response, APOE, cholesterol, and oxidative stress.
• Therapeutic possibilities: NSAIDs, cytokine blockade, immunotherapy, diet.
Recent findings: Results are provided from only two recent prospective cohorts of older Americans and French individuals (>=65 years) on the relationship of Mediterranean diet to cognitive functions. A high adherence to the Mediterranean diet has been associated with slower cognitive decline, with reduced risk of mild cognitive impairment conversion to Alzheimer's disease and with reduced risk of Alzheimer's disease.
**Prospective association studies** (re modifiable risk factors for MCI and dementia/AD and progression of MCI to AD) would include the following baseline variables:

1) vascular risk factors: baseline systolic and diastolic BP, BMI, abdominal obesity, fasting glucose levels and serum lipid levels. These factors will be analysed alone or clustered in the concept of metabolic syndrome.
2) lifestyle factors: physical activity, alcohol consumption and smoking, analysed using quantitative information collected at baseline. MNA and FFQ will be administrated.
3) antioxidants: plasma level of different tocopherols and tocotrienols; carotenoids; coenzyme Q10.

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Intervention studies on Zabut population

- D-lemonina (terpene)
- Pro-prebiotici?
- Integratori?
- Flavonoidi?
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• Roberto Monastero (Neurologia & statistica) Laboratorio di Epidemiologia e Psicologia dell’invecchiamento e delle Demenze, Dipartimento di Neuroscienze, Università di Palermo

• Sonya Vasto (Immunologia, microbiologia e nutrizione) Dipartimento di Biopatologia e Biotecnologie mediche e forensi, Università di Palermo.
THANK YOU FOR YOUR ATTENTION