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Innate Immune Responses in the Geriatric Population

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1. Introduction

Demographic evolution represents a challenge for public health. Global population, especially in the developed countries is aging. The proportion of the population above 60 years has increased from 8% in 1950 to 10% in 2000 and is expected to reach 21% by 2050. Older people suffer from more frequent and more severe community-acquired and nosocomial infections than younger people. The clinical presentation is often atypical making diagnostic more difficult. “Latent” intracellular pathogens such as viruses (Herpesviridae) or Mycobacteriae are more prone to reactivate while opportunistic infections (such as Candida) manifest at increased rates (Ongradi & Kovesdi, 2010). Older individuals suffer from reactivation of mycobacterium tuberculosis that counts for 15 percent of all geriatric pulmonary infections. There is also an age-related decline in the magnitude of the responses to vaccination. Low-level chronic inflammation, a process referred to as “inflamm-aging”, is commonly observed in older people. It results in both decreased immunity to exogenous antigens and increased autoreactivity. It is well documented that a significant fraction of older people are positive for low affinity autoantibodies without clinical significance. Rheumatoid factors are present in up to 5% of young healthy individuals, a proportion that increases up to five times in older persons. Similarly, the prevalence of antinuclear antibodies is higher in healthy individuals over 70 years of age compared to healthy young adults (Grolleau-Julius et al., 2010). Furthermore, older persons are more susceptible to develop cancer, probably because of accumulation of cell damages and reduced “immunosurveillance” (Malaguarnera et al., 2010; Fulop et al., 2010).

There is clear evidence of an age-related decline in effectiveness of the immune system in humans; it is common to most if not all vertebrates and to some invertebrates. For example, drosophilae display pro-inflammatory status with increasing age and have reduced capacity to produce antimicrobial peptides in response to infection. There is also substantial body of evidence reporting immunosenescence in wild birds (decline of T- and B-cell functions and altered innate immune responses) and mice (thymic atrophy and reduced recent thymic emigrants) (Shanley et al., 2009). Immunosenescence is characterized by the deleterious “filling” of the immunological space with memory and effector cells as a consequence of exposure to a variety of antigens. The continuous attrition caused by clinical and subclinical

infections as well as the continuous exposure to other types of antigens (food, allergens) is likely to be responsible for the chronic activation of the immune system and inflammation. Immunosenescence process along with morbidity and mortality will be accelerated in those subjects who are exposed to an extra-burden of antigenic load. The phenomenology of HIV+ patients after several years of infection shows striking similarities (regarding T cell subset rearrangement, T cell clonal expansion, and telomere shortening) with that observed in the context of aging. It is tempting to speculate that chronic infections with other micro-organisms could also lead to this process (De Martinis et al., 2005).

Many studies have tried to collect immune data in older people to establish reliable “biomarkers of aging”. However, the literature is full of confusing and conflicting data. There are many difficulties in interpreting immunogerontological observations. The major concern is the way “young” and “old” populations are defined in these studies. On one hand, restricting selection to only “healthy” older people might introduce a bias and not be representative of the general population. On the other hand, comorbidities that are encountered in the geriatric population will certainly affect many parameters of the immune responses. Some studies try to restrict inclusion criteria to better characterize age-associated alterations of immunity such as the SENIEUR protocol (Wikby, 2008; Chen et al., 2009; Ligthart et al., 1984). Unfortunately, it does not represent our geriatric population (only 10% of older people meet the criteria) (Chen et al., 2009). OCTO study was less restrictive for inclusion criteria, admitted 400 octogenarians that were not institutionalized, had no or only mild cognitive dysfunction and were not on drug regimen that might have influenced the immune system. This study predicts the same **immune risk profile (IRP)** of subsequent 2 year-mortality than SENIEUR protocols characterized by high level of CD8 T cells, inversion of the CD4+/CD8+ T cell ratio, poor mitogen stimulated lymphoproliferative responses and loss of CD28 costimulatory molecule (table 1).

Immune Risk Phenotype (IRP)
<ul style="list-style-type: none">- Low levels of B cells- Inversion of the CD4+/CD8+ ratio- Poor mitogen stimulated lymphoproliferative response- Increased levels of CD8+ CD28- CD57+ T cells- Positive serology for Cytomegalovirus

Table 1. The “immune risk phenotype”.

Finally, the NONA study did not exclude individuals because of compromised health to place immune risk phenotype in a broader context of health and cognitive dysfunctioning. It confirmed the OCTO study and demonstrated that the immune risk phenotype concept could be generalized to a sample of nonagenarians not specifically selected for good health at baseline (Pawelec et al., 2005; Wikby, 2008). Both studies demonstrated that aging is associated with low-grade inflammation and that inflammatory markers like increase of IL-6, C-reactive protein (CRP) and decrease of albumin are significant predictors of mortality in very old humans independently of disease and comorbidity (Wikby, 2008). The new HEXA study

examined the IRP profile in hexagenarians and shows the same characteristics than in the very old. The study has now to examine the impact of the IRP on morbidity and mortality in this age group (Wills et al., 2011).

Herein, we will first review the major changes in adaptive immune responses observed in the geriatric population. We will then focus on what is known about innate immune responses in this age group. Finally, we will discuss the links between the specific clinical context of aging and alterations of immune responses.

2. Adaptative immune responses: thymic involution, T cell exhaustion and persistent infections

2.1 Thymic involution

The thymus is the site of T cells differentiation and maturation and is often referred to as the “immunologic clock” of aging. Age-associated thymic involution is a well-recognized factor associated with immunosenescence, and in particular with reduced vaccine efficacy. The thymus undergoes a progressive involution and the output of new cells falls significantly. Thymic functions already start decreasing after one year of life but the process becomes significant after 40 years of age. The expansion of perivascular space (adipocytes, peripheral lymphocytes, stroma) with age is such that thymic epithelial space represents less than 10% of the total thymic tissue by 70 years of age. When extrapolated, data suggest that the thymus would cease to produce new T cells by 105 years of age (Boren & Gershwin, 2004; Ongradi & Kovesdi, 2010; Gruver et al., 2007). There might be a benefit for the organism to reduce cell proliferation within the thymus, once a T-cell repertoire is established, so that energy can be devoted to other physiological processes (Shanley et al., 2009). Both intrinsic and extrinsic factors are thought to be involved in this process (Boren & Gershwin, 2004). Thymic epithelial cells produce a number of factors that can be thymosuppressive (Interleukin (IL)-6, LIF, OSM) or thymostimulatory (interleukin (IL)-7, Keratinocyte growth factor, Thymic stromal lymphopoietin, growth hormone, leptin). Thymic atrophy is mediated by upregulation of thymosuppressive and decrease of thymostimulatory cytokines such as IL-7. This cytokine plays an important role for thymus function maintenance; it promotes thymopoiesis by maintaining anti-apoptotic protein Bcl-2 and inducing V-DJ recombination (Ongradi & Kovesdi, 2010; Gruver et al., 2007). Extrathymic factors including zinc, thymulin, cathepsin L, melatonin, thyroid hormone, growth hormone also contribute to thymus function. Stressful events, such as infections, septic shock, malnutrition, pregnancy, chemotherapy or irradiation have been associated with reversible thymic involution. Exogenous administration of leptin prevents this stress-induced thymic involution in mice, suggesting possible therapeutic intervention in aged humans (McElhaney & Effros, 2009; Boren & Gershwin, 2004; Gruver et al., 2007; Gruver et al., 2009; Hick et al., 2006). However, it is unclear whether age-associated and stress-induced thymic involutions result from the same mechanisms (McElhaney & Effros, 2009; Boren & Gershwin, 2004; Gruver et al., 2007). “Thymic rejuvenation” techniques have been sought for many years. Keratinocyte growth factor, IL-7 and ghrelin are interesting candidates (McElhaney & Effros, 2009; Aspinall et al., 2007). Keratinocyte growth factor enhances IL-7 production in the thymus, promoting development and maintenance of T cells following vaccination. IL-7 treatment has been shown to increase thymic output and number of central memory T cells and improve the antibody response to influenza vaccination in aged rhesus

macaques (McElhaney & Effros, 2009). Intrathymic infection with IL-10-expressing adenovirus can prevent thymocyte apoptosis induced by sepsis in mice (Ongradi & Kovesdi, 2010; Gruver et al., 2007).

Thymic involution causes a continuous drop in the output of recent thymic emigrants while homeostatic mechanisms attempt to maintain constant peripheral T cell numbers. Consistent with greater proliferative history, naïve T cells from elderly have less T cell receptor excision circle (TREC) numbers and shorter telomere length (see below) (Ferrando-Martinez et al., 2011). However, the total number of T cells shows very little decline with advancing age, except in the very old. Furthermore, the proportion of naïve and memory T cells is well maintained up to the age of 65 years. It has been postulated that the majority of naïve T cells in the adult are generated by cell division of existing T cells, rather than thymic export. The repertoire of naïve CD4 T cells is also very well maintained up to the age of 65 years. It then dramatically dwindles and is found to be severely contracted and undistinguishable from the repertoire of memory T cells at 75-80 years of age. The same phenomenon is shown for naïve CD8 T cells. IL-7 plays an essential role in controlling homeostatic proliferation of naïve CD4+ and CD8+ T cells (Ferrando-Martinez et al., 2011; Arnold et al., 2011; Naylor et al., 2005; Kilpatrick et al., 2008).

Main lymphocyte subsets	
T lymphocytes cells (CD3+):	CD4+ helper T cells
	CD8+ cytotoxic T cells
	CD25+ Regulatory T cells
B lymphocytes cells (CD19+)	Naïve B cells
	Memory B cells
	Plasmacytes
Natural killer (NK) cells and NKT cells	
γδ T cells	

Table 2. Main lymphocyte subsets.

2.2 T lymphocytes

Memory and naïve human T cells are distinguished by their expression of members of the CD45 family surface antigens. CD45RA antigen is expressed primarily on naïve T lymphocytes and CD45RO is present on the cell surface of memory T lymphocytes (Figure 1). With normal aging, the slow turnover and long lifespan of naïve T cells are preserved but thymus output diminishes gradually and ultimately becomes insufficient to replace naïve T cells lost from the periphery. Conversely, cumulative chronic exposure to pathogens and environmental antigens promotes the accumulation of memory cells and eventually a state of “exhaustion”. This phenomenon is associated with increased complication risk following viral illnesses such as influenza, respiratory syncytial virus and reactivation of herpes viruses (McElhaney & Effros, 2009; Desai et al., 2010).

In aged mice, formation of “immunological synapse” between CD4 T cells antigen presenting cells is hindered. This has been related to altered cholesterol/phospholipid ratio in lymphocyte membranes, leading to impaired T cell receptor (TCR)-dependent recruitment of signal molecules to the immunological synapse. In humans, alteration in the cholesterol/phospholipid ratio of lymphocyte membranes has also been documented and is associated with reduced proliferation rate (Arnold et al., 2011; Huber et al., 1991; Stulnig et al., 1995). With age, human and murine T cells tend to secrete less IL-2, an observation linked to important alterations in the proximal TCR signalling pathway (Boren & Gershwin, 2004; Fulop et al., 2007; Chakravarti & Abraham, 1999). Peripheral blood lymphocytes from aged individuals also display decreased NFAT expression, a key transcription factor implicated in IL-2 gene activation (Rink et al., 1998; Mysliwska et al., 1998; Wikby et al., 1994; Desai et al., 2010; DiPenta et al., 2007). However, when only “healthy older” people are considered (SENIEUR protocol), production of IL-2 was not different from that observed in younger individuals (Chen et al., 2009).

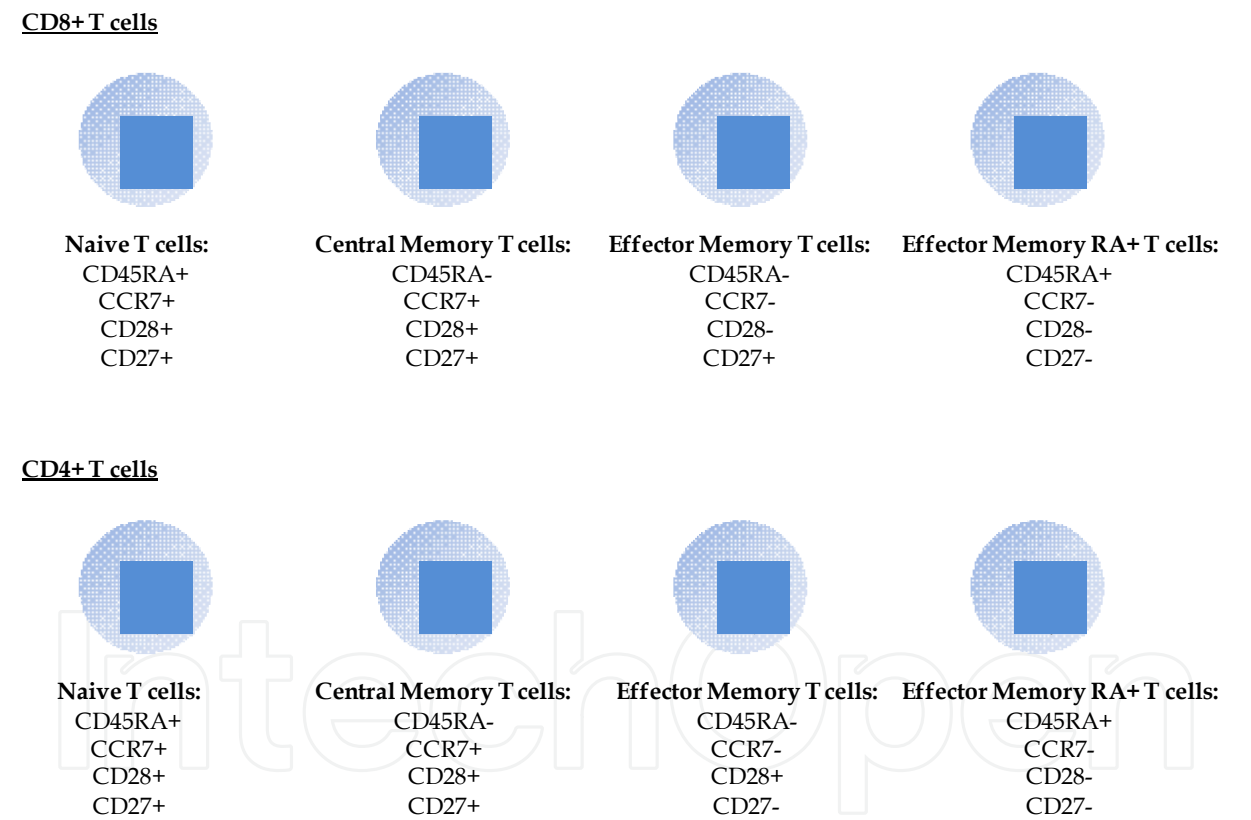


Fig. 1. Phenotype of different lymphocytes T cells subsets.

CD4 T lymphocytes from aged mice display decreased CD40L expression. In humans, CD40L expression is also reduced on peripheral blood CD4 T cells upon anti-CD3 stimulation in old people compared to younger individuals (Fernandez-Gutierrez et al., 1999). As this molecule is critical for B-T cell interactions, it could participate to the alteration of humoral responses observed in the old population. The function of “follicular helper T cells” in older people should be revisited in the light of the recent advances in the field (Ongradi & Kovesdi, 2010; Gruver et al., 2007; Crotty, 2011).

2.2.1 Naïve T cells

Naïve T cells from young and old adults differ significantly. Compared to young adults, 40% of human naïve CD8⁺ CD28⁺ T cells of older people do not express CD62L and CCR7, two receptors implicated in the migration to peripheral lymphoid tissues (Ongradi & Kovesdi, 2010; Aspinall et al., 2007). In humans, naïve CD8 T cells seem to be more susceptible to death receptor-mediated apoptosis and are more affected by age-related changes than the CD4⁺ T cell pool (Gupta & Gollapudi, 2006; Gupta & Gollapudi, 2008). CD45RA⁺CD28⁺CD8⁺ T cells from older people produce larger amounts of interferon (IFN)- γ upon polyclonal stimulation than those from young persons (Pfister & Savino, 2008).

As mentioned earlier, IL-7 plays an essential role in controlling homeostatic proliferation of naïve CD4⁺ and CD8⁺ T cells and supports the survival of naïve CD8⁺ T cells. IL-7 acts in conjunction with T cell receptor signals from contact with self-MHC/peptide that sustain the expression of anti-apoptotic molecules. However, this extended lifespan of naïve T cells could be associated with prolonged exposure to unfavourable environmental factors which cause DNA damage and contribute to decreased function in old age (Arnold et al., 2011).

2.2.2 Memory T cells

The three protocols (SENIEUR, OCTO and NONA) compared immune risk phenotype in older people with different state of comorbidities. Aging is associated with an increase of memory cells, a decrease of naïve T cells and a loss of CD28 molecules. Chronic cytomegalovirus (CMV) infection has been proposed as the main stimulus driving the *in vivo* process of “replicative senescence” (see section 4.3). CMV is associated with clonal expansion of CD8 T cells, increased numbers of CD8⁺ CD28⁻ T cells, largely terminally differentiated effector memory T cells expressing CD45RA CCR7⁻ (effector memory T cells, “EMRA”) and inverted CD4:CD8 ratio (McElhaney & Effros, 2009; Pawelec & Derhovanessian, 2011; Pawelec et al., 2005; Derhovanessian et al., 2010). This will be further developed in this chapter.

Much effort has been dedicated to characterize cellular markers of immunosenescence. While T cell receptor repertoire contraction is a characteristic of the aging immune system, there is increasing evidence that clonal T cells of older persons may express a variety of receptors normally found on natural killer (NK) cells such as CD16, CD56, CD57, CD94, CD161, NKG2D and KIR family. NK receptors expression can have profound impact on immunity. Whereas, NK receptors diversity defines functional subsets of NK cells that contribute to normal innate antigen-independent responses, it is proposed that NK receptors expression on T cells from aged individuals is an adaptive mechanism of immunological diversity in the midst of a contracting T cell receptor repertoire. Studies with *in vitro* replicative senescence systems indicate stable NK receptors expression on T cells follows the loss of CD28 (Abedin et al., 2005; Alonso-Arias et al., 2011; Rajasekaran et al., 2010). Expression of CD57 is also found on T lymphocytes, where it is currently considered as a marker for “replicative senescence” (also termed “clonal exhaustion”) i.e., a high susceptibility to activation-induced cell death and the inability to undergo new cell-division cycles despite preserved ability to secrete cytokines upon encounter with their cognate antigen. The phenotypes associated with replicative senescent CD8⁺ T lymphocytes are not

well defined but are generally attributed to lack of CD28 or expression of CD57. CD8+CD57+ T lymphocytes have high cytotoxic effector potential including perforin, granzymes and granulysin. At the messenger and protein levels, CD8+CD57+ T lymphocytes express more adhesion molecules and fewer chemokine receptors (CCR7 and CXCR4) than CD8+CD57- T lymphocytes but preferentially express CX3CR1. The lower expression level of genes involved in cell-cycle regulation supports the limited proliferation capacities of CD8+CD57+ T lymphocytes, even in response to polyclonal or cytokine stimulation (Focosi et al., 2010).

As detailed below, these CD8+CD57+ T lymphocytes are commonly found in individuals with chronic immune activation and increase in frequency with age (from absence in newborns to 15–20% of circulating CD8 T cells), but the percentage of CD8+CD57+ cells increases in a series of clinical conditions whose common denominator is functional immune alteration, including HIV and CMV infections, common variable immunodeficiency, hematological cancers and autoimmune diseases (Pawelec & Derhovanessian, 2011; Focosi et al., 2010). OCTO, NONA and SENIEUR protocols conclude that the number of cells in the CD57+CD28-, CD45RACD27- and CD57+CD56+CD8+ T cells subsets in older people were independent of the individual's health status (disease interfering with immunity were excluded) (Nilsson et al., 2003). In older humans, CD4 T cells also express more NKG2D molecules and are associated with replicative senescence. NKG2D+ CD4+ T cells are mostly CD28- CD4+ T cells and also present cytotoxic properties (Alonso-Arias et al., 2011). These senescent cells resulting from permanent immune activation are potent producers of proinflammatory cytokines and have shorter telomeres than NKG2D- CD4+ T cells (Ongradi & Kovesdi, 2010; Gruver et al., 2007). Immune phenotype of T cells is correlated with individual "fitness" in individuals over 78 years. Unimpaired aged individuals display T cells expressing inhibitory NK receptors (CD158a, CD158e and NKG2a) and functionally impaired aged individuals display T cells expressing stimulatory NK receptors (CD56, CD16, NKG2D) (Vallejo et al., 2011).

It has been shown that high proportions of CD8+ CD25+ memory T cells are associated with healthy aging and are rare or absent in older people with latent CMV infection. The presence of CD8+CD25+ T cells is associated with the maintenance of intact humoral responses. They produce IL-2 and IL-4, assist B memory generation, induce MHC II upregulation on B cells, and promote antibody isotype switching to IgG1 and IgE. These T cells coexpress CD4 molecule and present a highly diverse TCR repertoire and longer telomere compared to the CD8+ CD25- subset (Herndler-Brandstetter et al., 2005).

Aged individuals (more than 65 years) have an increase in peripheral blood regulatory T cells expression. The increase of this population seems to be linked to the healthy state of elderly people. The *in vitro* function of this population is not altered with age (Ongradi & Kovesdi, 2010; Gruver et al., 2007; Gregg et al., 2005).

$\gamma\delta$ T cells represent a minor population of human peripheral lymphocytes (1–10%). They play a role in antiviral and antitumoral immunosurveillance. They produce high levels of cytokines, mainly TNF α and IFN γ . With increasing age, the absolute number of $\gamma\delta$ T cells and their proliferation rate is reduced while they express more TNF α . Inversely, they present no change in IFN γ expression and cytolytic activity with age (Argentati et al., 2002).

2.3 B lymphocytes and humoral responses

B cells also present alterations with increasing age. Decreased IL-7 production provokes a reduced ability to support B cell expansion by bone marrow stromal cells (Ongradi & Kovesdi, 2010). Bone marrow contains pluripotent stem cells that mature into bone tissue and cells that form peripheral blood cells, which further develop in specialized secondary compartments into functional immune cells. The stroma matrix of the bone marrow compartment is composed of accessory cells such as megakaryocytes, osteoblasts, osteoclasts, adipocytes, chondrocytes, myoblasts and fibroblasts. The hematopoietic compartment decreases with increasing age and is replaced by adipose tissue. Surprisingly, increased number of bone marrow resident macrophages is observed with age but these cells have decreased ability to secrete TNF α . Both TNF α and IL-1 are essential to promote secretion of other cytokines critical to stromal integrity, such as IL-6, IL-11, M-CSF or GM-CSF. There is no clear evidence that hematopoietic cells number (CD34+) decreases with age. Hematopoietic cells give rise into common lymphoid progenitors like pro-B cells. There are discrepancies about the evolution of pro-B cells with age. Conversely, pre-B cells decrease markedly with age (Gruver et al., 2007).

The proportion and numbers of total B cells (CD19+) decrease with age. Data on specific B cell subsets is less clear. Naïve B cells are defined as IgG- IgA- IgD+ CD27- whereas memory B cell population is very heterogeneous, comprising three subtypes (Figure2): “IgM memory” cells (that are IgD+ IgM+ CD27+, important against bacterial infections), “classical switched memory” (IgG+/IgA+ CD27+) and “double negative” B cells (IgG+/IgA+, IgD- CD27- B cells). This later group could emerge independently from T cell help.

B lymphocytes:

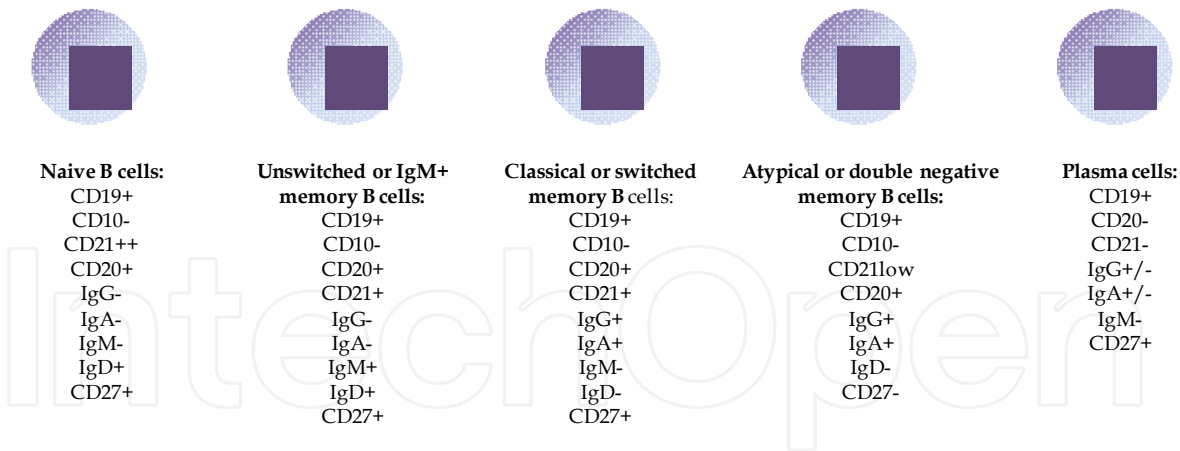


Fig. 2. Phenotype of different B lymphocyte cells subsets.

Proportion of naïve B cells decreases with age. Several reports indicate that the proportion and number of CD27+ (memory) B cells increase but other reports show the opposite (Bulati et al., 2011; Colonna-Romano et al., 2009). The discrepancy probably reflects differences in the subsets definition and study protocols. Naïve B cells exhibit a reduced susceptibility to apoptosis in aged individuals (Chong et al., 2005). B cells produce large amounts of proinflammatory cytokines upon CD40 and IL-4 activation and so could play a role in the generation or in the maintenance of the inflammatory environment of the older people (Buffa et al., 2011). The “IgM memory” subset decreases with age. Other reports indicate a

decrease of “switched memory” B cells. Finally the proportion of “double negative” B cells seems to increase with age (Ademokun et al., 2010; Bulati et al., 2011; Colonna-Romano et al., 2003; Colonna-Romano et al., 2009; Chong et al., 2005). This “double negative” population in aged individuals presents reduced expression of CD40, HLA-DR and CD80 and shorter telomeres. These cells are also present in patients with systemic lupus erythematosus (Colonna-Romano et al., 2009). There is a significant increase of anergic, “exhausted” memory cells with CD27 downregulation (CD27-) in older people. In centenarians, naïve B cells (IgD+ CD27-) are more abundant whereas exhausted memory cells (IgD- CD27-) do not show the increase previously demonstrated in healthy older people. Authors conclude that the reservoir of naïve B cells might be one factor of “successfully aging” (Ongradi & Kovesdi, 2010; Fernandez-Gutierrez et al., 1999).

B cells progenitors undergo maturation and differentiation in secondary lymphoid tissue, such as spleen and lymph nodes. Spleen arteries are surrounded by T lymphocytes in the periarteriolar lymphoid sheath. Primary lymphoid follicles containing B cells are adjacent to the periarteriolar lymphoid sheath. Other cell types such as T cells, dendritic cells and macrophages make up the marginal zone. This constitutes the white pulp. Age-associated architectural changes have been documented. Spleen from aged humans demonstrates a decrease in arterial vessels and an increase in stromal cells over lymphocytes. Total splenic weight increases with age due to fibroblastic infiltration (Gruver et al., 2007).

The germinal centre reaction is essential for the generation of high affinity antibody in response to infectious agents. This process is accomplished by two distinct mechanisms: class switch recombination, which enables B cells to change antibody isotype, and somatic hypermutation, the process of introducing mutations into the B cell receptor to increase antigen affinity. Data indicate that there is no change in the fundamental mechanisms of somatic hypermutation with age in man but an impaired ability of class switch recombination has been described in aged mice (Ademokun et al., 2010).

There is also a collapse in B cell receptor repertoire diversity with age and an expansion of monoclonal cells. The incidence of “monoclonal gammopathy of undefined significance” (MGUS) has been shown to increase with age. Sensitive assays reveal that as many as 50% of old mice and 20% of elderly humans have serum monoclonal immunoglobulin. As half of serum monoclonal immunoglobulins reacts with autoantigens, it appears that cells producing monoclonal immunoglobulins are drawn preferentially from the population of “B1 cells” that expand with age in both humans and mice (Weksler & Szabo, 2000). These CD5+CD20+ cells are produced during fetal life and are T-independent (in contrast to CD5-CD20+ “B2 cells” that are produced post-natally and are T-dependent). In humans, approximately 1% of old subjects with serum monoclonal immunoglobulin develop multiple myeloma each year, derived probably from plasma cell clonal expansions. Chronic lymphocytic leukemia, another lymphoid malignancy that occurs late in life, may arise from malignant transformation of the large B-cell clonal expansions. Chronic lymphocytic leukemia is frequently associated with T-cell abnormalities, including an inversion of the normal CD4 to CD8 T cell ratio, expansions of large granular lymphocytes, and clonal expansions of CD4 and CD8 T cells. These T-cell clonal expansions may represent a clonotypic response to transformed B cells or their secreted immunoglobulins. This hypothesis is supported by the finding that T cells from myeloma patients can be activated by monoclonal Ig fragments (Ademokun et al., 2010; Bulati et al., 2011; Colonna-Romano et

al., 2003; Weksler & Szabo, 2000). However, in humans, despite the reduced number of B cells and the defects in class-switching, serum IgG, IgA are increased with age; IgD levels decrease with age but IgE and IgM remain unchanged or are decreased. IgG1 and IgG3 (in men) subtypes are also increased with age (Ademokun et al., 2010; Bulati et al., 2011; Colonna-Romano et al., 2003).

The quality of the humoral response also declines with age, characterized by lower antibody responses and decreased production of high affinity antibodies. B cells from aged individuals can be directly activated by cytokine but are weakly activated by anti-CD3 activated PBMCs. This result suggests that poor B cell responses is a consequence of inadequate help from T cells (Ongradi & Kovesdi, 2010; Fernandez-Gutierrez et al., 1999). In mice, aged CD4⁺ T cells provide poor assistance in germinal centres and promote low-affinity antibody production. Furthermore, overproduction of Th2 cytokines could augment B cell-mediated autoimmune disorders by enhancing the production of autoreactive antibodies. The percentage of naïve follicular B cells declines whereas subsets of antigen-experienced mature B cells with longer life span increase including poly/self reactive subtypes. These cells may be reactivated due to age-associated reduced tolerance or loss of tissue integrity leading to the exposure of neo-self antigens that results in aberrant autoimmune response (Ongradi & Kovesdi, 2010). Taken together, these data indicate that in older people, B cell repertoire diversity is limited while there is an increase of polyspecific and auto-antibodies.

3. Innate immune responses and aging.

3.1 Monocytes and dendritic cells subsets, neutrophils

Monocytes represent about 5-10% of peripheral blood leukocytes in humans. They originate from a myeloid precursor in the bone marrow, circulate in the blood and spleen then enter tissues. Monocytes represent circulating precursors for tissue macrophages and dendritic cells. The differential expression of CD14 (part of the receptor for LPS) and CD16 (also known as FcγRIII) are commonly used to define two major subsets (Figure 3): “classical” CD14⁺⁺ CD16⁻ cells, representing 95% of monocytes in healthy individuals and the “non-classical” CD14⁺ CD16⁺ comprising the remaining fraction. This later population is considered to represent activated cells that have undergone CD16 upregulation and CD14 downregulation and have been implicated in the pathogenesis of atherosclerosis. In healthy older volunteers, there is a shift of “classical” to “non-classical” monocytes. While “classical” monocytes express CCR2, “non-classical” monocytes preferentially express CX3CR1. Expression intensity of CXCR3 tends to decrease with age (Seidler et al., 2010; Sadeghi et al., 1999).

Dendritic cells (DCs) play a key role in the immune system since they orchestrate initiation, amplification and suppression of immune responses. In particular, maturation of DCs is crucial for the initiation of immunity. In fact, immature DCs are extremely efficient in capturing and processing antigens, but their unique ability to potently activate naïve T lymphocytes is acquired after maturation. This process is accompanied by the up-regulation of major histocompatibility complex molecules and the increased expression of membrane molecules that interact with T lymphocytes to enhance cell activation and adhesion. Furthermore, DC maturation leads to the release of high levels of cytokines that are

Main subsets of blood innate immune cells	
Granulocytes :	
Neutrophils	
Eosinophils	
Basophils	
Monocytes :	
« Classical » monocytes :	
CD16- CD14++	
Inflammatory monocytes :	
CD16++ CD14+	
CD16++ CD14-	
Dendritic cells :	
Plasmacytoid DC	
CD123+ CD11c-	
Myeloid DC	
CD123- CD11c+	

Table 3. Blood innate immune cells.

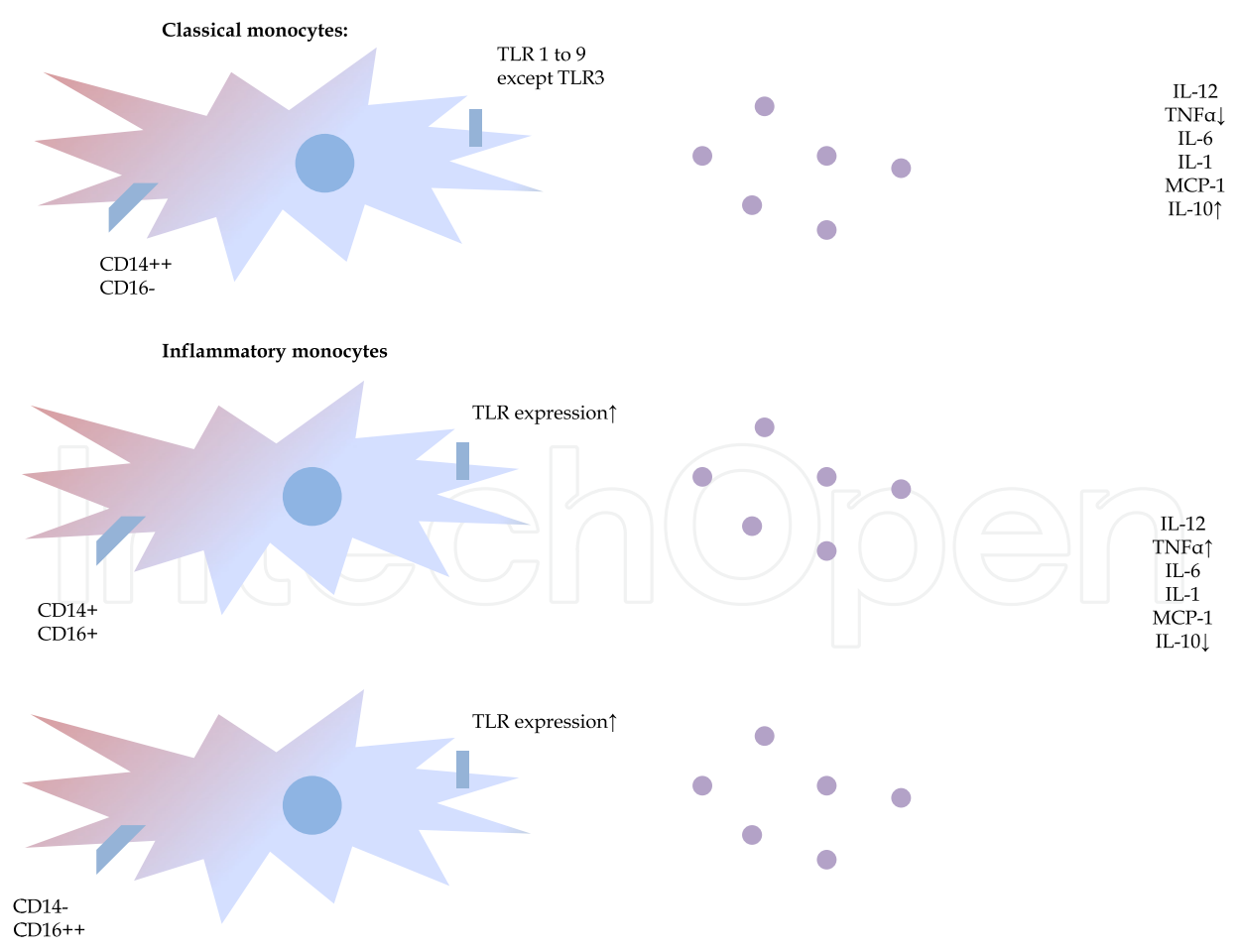


Fig. 3. Major subsets of monocytes.

responsible for the regulation and polarization of both innate and acquired immune responses (Ciaramella et al., 2011; Agrawal et al., 2007a). DCs are heterogeneous and are subdivided into two major categories: those that are present in peripheral blood (myeloid and plasmacytoid DCs) and those that are present in tissue/organs (Langerhans cells, interstitial and interdigitating DCs) (Agrawal et al., 2007b). Myeloid DCs express CD11c+ and low level of CD123 and can be subdivided into CD16+ (40-80%), CD1b/c+ (20-50%) and BDCA3+ (2-3%) subpopulations (Figure 4). Plasmacytoid DCs express low level of CD11c, high level of CD123, BDCA2 and BDCA4 and are specialized for production of type I IFNs in the context of viral infections (MacDonald et al., 2002; Dzionek et al., 2000).

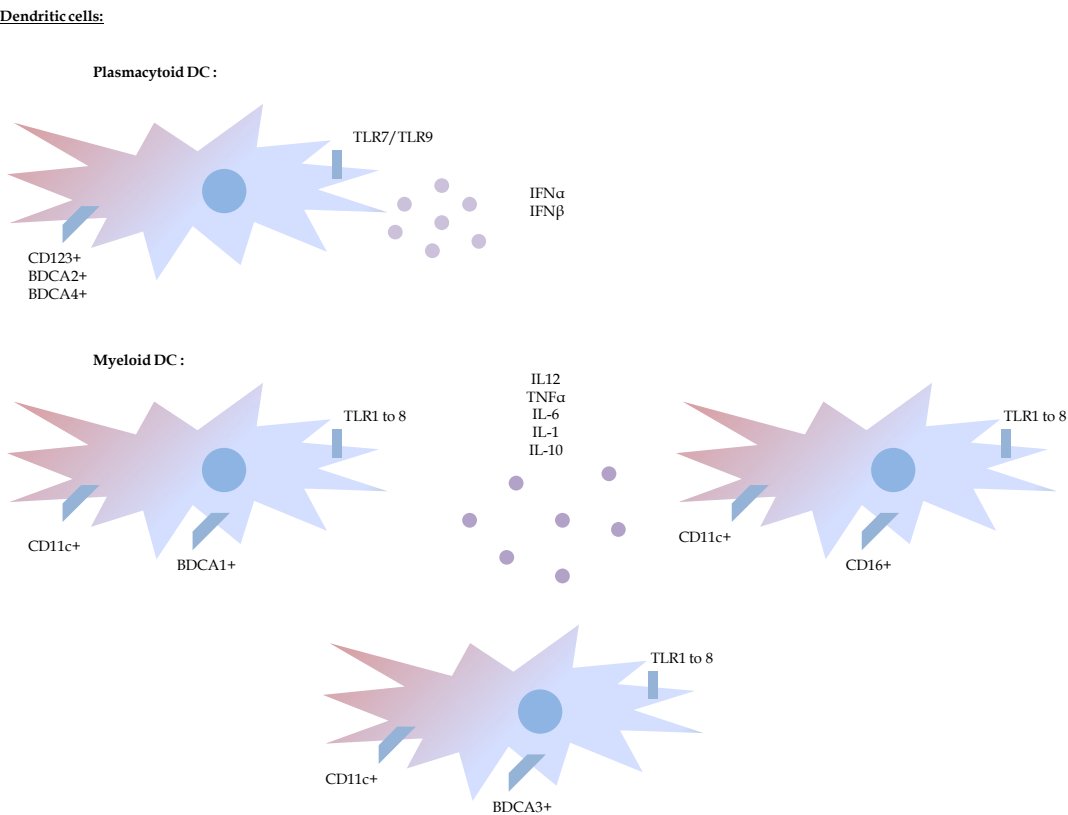


Fig. 4. Major subsets of dendritic cells.

In vitro monocyte-derived DCs, cultured with GM-CSF+IL-4, are closely related to interstitial or myeloid DCs (Agrawal et al., 2007b). Several studies used these *in vitro* cultured cells to assess the phenotype and functions of DCs in aged populations. Monocyte-derived DCs present no clear differences of costimulatory or activatory molecules (HLA-DR, CD80, CD86, CD40, CD83) except for CD25 and ICAM after lipopolysaccharide stimulation in healthy older individuals compared to younger (Agrawal et al., 2007b; Ciaramella et al., 2011; Agrawal et al., 2007a). Monocyte-derived DCs of older people are less efficient for micropinocytosis and phagocytosis of apoptotic cells and are impaired for migration (Agrawal et al., 2007b).

Several reports indicate that there are no significant differences in numbers of circulating myeloid and plasmacytoid DCs between older people and young subjects and that the

expression of costimulatory molecules (CD86 and HLA DR) is similar (Agrawal et al., 2007a; Agrawal et al., 2007b; Pietschmann et al., 2000). In contrast, another study showed that numbers of myeloid DCs progressively declined with age while proportion of plasmacytoid DCs was unaffected. Peripheral blood DCs from healthy old subjects expressed CD86 and CD83, two markers of activation, on a higher percentage of cells, in comparison to young subjects. Maturation with lipopolysaccharide was unaffected with age (Della et al., 2007). Other studies showed reduced numbers of plasmacytoid DCs but not of myeloid DCs in healthy aged blood donors. Absolute numbers of circulating myeloid DCs is affected by declining health status (Perez-Cabezas et al., 2007; Panda et al., 2010; Shodell & Siegal, 2002; Jing et al., 2009). The use of Ficoll-enriched cells versus whole blood, differences in sample sizes, age groups, health status, genetic factors and subset definitions may contribute to the inconsistent findings with age in these studies. Taken together these data suggest that many factors, in addition to age itself, probably influence absolute/relative numbers or activation status of circulating DCs in geriatric populations.

Neutrophils are key players for early responses to bacterial infections. They rapidly produce reactive oxygen and nitrogen species when pathogens are encountered and produce many pro-inflammatory mediators. Several studies have shown alterations of neutrophil functions with age. Data remain conflicting in the literature concerning their number and phagocytic functions. One suggested alteration is their propensity to undergo apoptosis because of augmented cell oxidative load and perturbation of anti-apoptotic/proapoptotic mechanisms (Tortorella et al., 2006). Several reports indicate reduced chemotaxis (Fulop et al., 2004), phagocytosis and production of superoxide anion. Negative feedback mechanisms could also be perturbed (Fulop et al., 2004; Wessels et al., 2010). In contrast, centenarians do not present neutrophil defects compare to old people for adherence, chemotaxis, superanion production (Wessels et al., 2010; Alonso-Fernandez et al., 2008); (Crichton & Puppione, 2006).

3.2 Toll-like receptors

Toll-like receptors (TLR) are expressed on a variety of cells including macrophages, monocytes, natural killer cells, DCs, B and T lymphocytes. To date, 10 TLR are functional in humans. Pathogen associated molecular patterns serving as TLR ligands include lipopolysaccharide (LPS) on gram (-) bacteria (TLR4), diacetylated (TLR2/6) and triacetylated (TLR1/2) lipopeptides, peptidoglycan (TLR2), bacterial flagellin (TLR5), nucleic acid and double-stranded RNA (TLR3), single stranded RNA (TLR7 and TLR8) and unmethylated CpG oligodeoxynucleotides (TLR9). Recognition of microbial components by TLR initiates MYD88 and TRIF-dependent signal transduction pathways that culminate in both the elaboration of proinflammatory cytokine responses (via NFκB-dependent pathways) and the upregulation of type I IFNs and IFN-dependent genes. TLR-dependent activation of antigen presenting cells is a crucial step not only for the innate response but also for the ensuing initiation of the adaptive immune response. Inherited defects in TLR signaling are associated with a greater susceptibility to bacterial (especially *Streptococcus pneumoniae*) and mycobacterial infection (Figure 5). Furthermore, TLR ligands as immunogens or adjuvants play an important role in mediating immune response to several human vaccines (Shaw et al., 2011; van Duin & Shaw, 2007).

Several studies in humans and mice have shown that TLR expression and functions tend to decline with age (van Duin & Shaw, 2007). Human monocytes from aged individuals

present lower surface TLR1 expression than their younger counterparts (van Duin et al., 2007). These studies revealed an age-associated reduction in TNF α and IL-6 after stimulation of the TLR1/2 heterodimer. Similar observations were also noted for TLR7-induced IL-6 production. There is a significant decrease in TLR-induced upregulation of CD80 in older compared to young for all TLR ligands (van Duin & Shaw, 2007; Shaw et al., 2011). Myeloid DCs show decreased expression of TLR1, TLR3 and plasmacytoid DCs a decrease of TLR7 and TLR9 in older people compared to young individuals (Panda et al., 2010; Jing et al., 2009). DCs from older donors had diminished late phase responses such as the induction of transcription factors STAT1 and IRF7 and lower expression of IRF1,

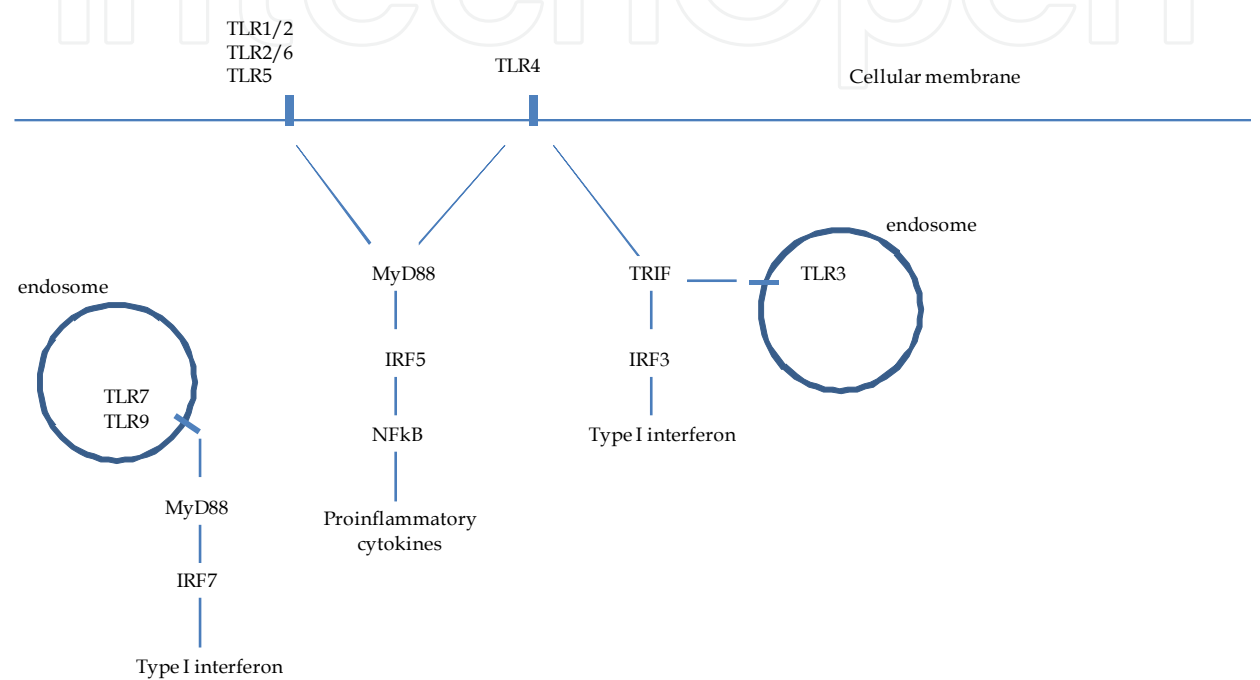


Fig. 5. Toll like receptor signaling.

suggesting a defective positive feedback regulation of type I IFN expression. Responses to TLR ligands may also be influenced by single nucleotide polymorphism within TLR genes. Authors report decreased IFN α , IL-6, IL-8 and TNF α in influenza virus-stimulated or HSV-2-stimulated plasmacytoid DCs from older compared to younger individuals (Shaw et al., 2011; Jing et al., 2009). IFN α production may be restored by zinc supplementation (Rink et al., 1998). Stimulated myeloid DCs and plasmacytoid DCs with different TLR ligands show a reduced expression of TNF α , IL-6, IL-12p40 and IFN α in healthy older people but an increased of the basal levels of this cytokine in older people (Panda et al., 2010). This decrease in TLR-induced cytokine production was strongly associated with the inability to mount protective antibody responses to the trivalent inactivated influenza vaccine currently recommended (Panda et al., 2010). LPS-stimulated monocytes from old people were reported to express less IL-12/23p40 levels in comparison to monocytes from young individuals (Della et al., 2007). However, their capacity to produce either bioactive IL-12 or IL-23 has not been addressed.

In contrast, analysis of monocyte-derived DCs from aged individuals revealed higher production of TNF α , IL-6 and IL-18 in response to LPS- and ssRNA but no difference in IL-

12p40/p70 (Ciaramella et al., 2011). There was no reduction of TLR4 expression with age but it was associated with decreased of phosphor-inositol 3(PI3) kinase, a negative regulator of TLR signalling. It manifested by decreased AKT phosphorylation and increased p38 mitogen activated protein kinase activation. They also present an increased expression of phosphatase and tensin homolog (PTEN), a negative regulator of PI3 kinase signalling pathway (Shaw et al., 2011; Agrawal et al., 2007a; Agrawal et al., 2007b).

Aging is generally associated with increased basal production of inflammatory cytokines but results of studies are often contradictory, depending on study designs and age groups (Beharka et al., 2001). Most studies report augmented plasma/serum levels of IL-6 and TNF α with increasing age, even in “selected” SENIEUR elderly over 85 years of age (Krabbe et al., 2004; Della et al., 2007). An elevated circulating IL-6 level is a strong predictor of thromboembolic complications while elevated TNF α levels are correlated with frailty (Krabbe et al., 2004). Another study shows that high basal IL-6 had a better predictive value for mortality than TNF α and that both cytokines were associated with classical risk factor like smoking, physical inactivity and body mass index (Bruunsgaard et al., 2003). A study confirmed increased serum IL-6, TGF β and s-ICAM in the older people but IL-6 increased also with poor health status (comparing SENIEUR, OCTO and NONA elderly) (Forsey et al., 2003; Mysliwska et al., 1998). Serum IP-10 and CXCL9 levels have also been reported with increasing age, in contrast to IL-10 and IL-12p40. These chemokines display strong chemoattractant activity for Th1 lymphocytes and have been involved in the pathogenesis of autoimmune disorders, such as Grave’s disease or Crohn’s disease, and in metabolic disorders, such as diabetes mellitus or atherosclerosis (Shurin et al., 2007). A recent study confirms that “impaired” (poor functional status) older people express higher basal levels of IFN γ , IL-12p70, IL-6 and TNF α while “unimpaired” older people express higher basal levels of IL-5 and IL-13 when compared to each other (Vallejo et al., 2011).

High basal production of pro-inflammatory cytokines is generally associated with poor capacity to respond to TLR stimulation (Bruunsgaard et al., 1999a). Indeed, several studies indicate that reduced responsiveness to LPS stimulation (lower TNF α , IL-1 β , IL-6, IL-10 and IL-1Ra production by whole blood cells) from 85-year olds is significantly associated with a worse survival and more risk factors like history of malignancies, chronic illness and elevated CRP levels (van den Biggelaar et al., 2004). Some whole blood studies however suggest that TNF α and IL-6 production upon TLR stimulation is increased in aged individuals, in particular for SENIEUR population under 85 years. This population probably does not display chronic low-grade inflammation (Gabriel et al., 2002). Zinc plasma levels could also represent an important factor to consider (Mariani et al., 2006).

IL-1 and TNF α are the earliest mediators of the acute phase response. Both cytokines induce a strong wave of cytokines including IL-6 and chemokines. In the course of *S. Pneumoniae* infection, inflammatory cytokines levels tend to persist for longer periods in older patients in contrast to younger ones (Bruunsgaard et al., 1999b). This observation could be related to increased pro-inflammatory environment in aged individuals but also to reduced clearing of the bacteria. It should also be interpreted in the light of possible alterations of renal function in the older people.

Taken together, low-grade chronic inflammation (“inflamm-aging”) seems to be a cardinal feature of advanced “healthy” aging. The magnitude of this process at a given age is

strongly influenced by multiple factors, including metabolic disorders and nutritional status. Indeed, poor health status and frailty will be associated with more intense inflammatory markers but poor responses to stimulation.

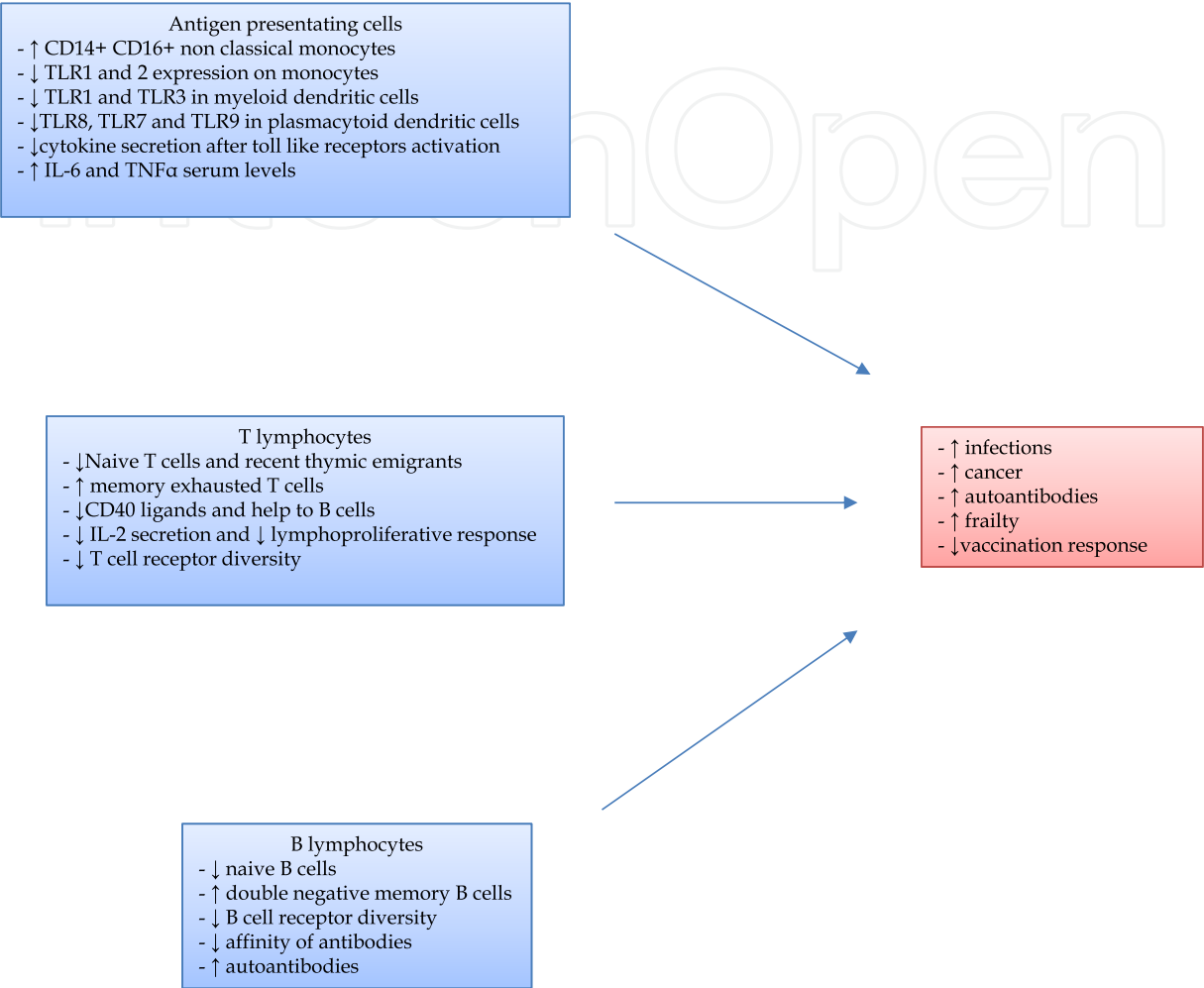


Fig. 6. Changes in immune responses observed in aged individuals.

4. Linking the characteristics of immune responses in the geriatric population to the clinical status.

“Normal” aging is determined genetically. At the cellular level, increased lifetime is associated with replicative-dependent shortening of chromosomal ends, also known as telomeres. In immune cells, this process is linked to immunosenescence. While this phenomenon is the normal destiny of dividing cells, it also reflects the global history of the organism. Here, we will discuss how the different immune parameters of the older people can be linked to the clinical characteristics encountered in the geriatric population.

4.1 Shortening of telomere length, genetic factors and hormonal changes

Telomeres consist of simple tandem DNA repeats (10-20kb) that do not encode for any gene products. The main function of telomeres is to cap the chromosome ends. Telomere capping

is necessary to distinguish the chromosome ends from DNA breaks within the genome. DNA breaks within the genome lead to cell cycle arrest and DNA repair or to induction of apoptosis when the damage is too severe. In contrast to DNA breaks, chromosome ends do not provoke DNA damage responses (Ongradi & Kovesdi, 2010; Jiang et al., 2007). Telomeres are regarded as the molecular clock of aging, including that of the immune system, especially for lymphocytes. Telomere shortening is due to the end replication problem of DNA polymerase at each round of cell division and to diminished activity of telomerase that fails to add telomere repeat sequence to the end of chromosomes. Telomerase is active during embryogenesis but is suppressed postnatally in most somatic tissues. In adult humans, telomerase stays only active in germ cells, certain stem cells and progenitor compartment. Telomerase reactivation occurs in activated lymphocytes and human cancer cells (Jiang et al., 2007; Ongradi & Kovesdi, 2010). Regulation of the telomerase activity is complex and is limited by expression of the catalytic subunit hTERT. Many transcription factors act as activators (including c-Myc, SP1, USF1/2, Ets, HIF-1, hALP) or repressors (p53, AP1, Mad1, Wilm's tumor 1, Smad3,...). Oestrogens activate c-myc thereby influencing telomerase activity. Indeed, women present longer telomeres than men. Cortisol inhibits telomerase activity in CD4 and CD8 T cells, suggesting a mechanism by which stress can negatively affect immune response (Andrews et al., 2010; Balasubramanyam et al., 2007). Chronic psychological stress in caregivers of Alzheimer's patients or chronically ill children is associated with telomere loss in peripheral blood lymphocytes, possibly explained by increased cortisol levels. Another study shows reduced telomerase activity related to neuroendocrine and psychosocial data indicative of greater stress (cortisol, epinephrine, norepinephrine) in women but they failed to show an association between telomere shortening and negative mood or education (Andrews et al., 2010; Jiang et al., 2007; Epel et al., 2006). In humans, telomeres shorten by 50-100 base pairs with each cell division. Most human tissues and organs show significant telomere shortening during aging, including peripheral blood mononuclear cells (PBMCs), isolated lymphocytes, kidney epithelium, vascular endothelial cells, hepatocytes, intestinal and lung epithelial cells, muscle but not for brain. Telomere length in PBMCs also correlated inversely with the mortality rate in 60-75 year olds. Individuals with short telomeres have a 3.18-fold higher mortality rates from heart diseases and 8.54-fold higher mortality rates from infectious diseases compared to those with relatively long telomeres but it is not a significant prognostic factor for survival above 85 years. In addition to telomere shortening with aging, accelerated shortening observed in PBMCs occurs in various human diseases such as myelodysplastic syndrome (Jiang et al., 2007; Andrews et al., 2010; Ohyashiki et al., 1999), atherosclerosis and hypertension (Jiang et al., 2007; Andrews et al., 2010; Benetos et al., 2004), coronary artery disease, human immunodeficiency virus, rheumatoid arthritis (Jiang et al., 2007; Andrews et al., 2010; Steer et al., 2007) systemic lupus erythematosus, cognitive decline,... (Jiang et al., 2007; Andrews et al., 2010). Alzheimer patients present reduced telomere length in PBMCs compared to control. There was also a significant correlation between T cell telomere length and MMSE score, CD28 expression and an inverse correlation between serum TNF α production and telomere shortening in T cells (Panossian et al., 2003). Telomere shortening is also correlated with duration of type 1 and type 2 diabetes and systolic blood pressure but not with diabetes complications (Astrup et al., 2010; Sampson et al., 2006). Another study confirms the negative correlation between cardiovascular risk factor or coronary heart disease and telomere length (Spyridopoulos et al., 2009; Brouillette et al., 2007). This study also shows that treatment with statins in patients

with high risk on the basis of telomere length results in substantial benefit effect (Brouillette et al., 2007). Oxidative stress is believed to be a major factor of accelerated aging, possible due to an increased pace of telomere shortening resulting from DNA damages observed upon smoking, obesity or cardiovascular diseases (Andrews et al., 2010; Balasubramanyam et al., 2007). The incidence of cancer sharply increases with aging. Telomere shortening appears to have a dual role in cancer formation. It was originally proposed that telomere shortening limits the lifespan of human cells thus acting as a tumor suppressor mechanism. The majority of human cancers exhibit very short telomeres, much shorter than the surrounding non-transformed tissue. However, more than 90% of human cancers show a strong reactivation of telomerase (Jiang et al., 2007).

Early studies showed that human somatic cells have a finite number of replicative cycles. The term “replicative senescence” is used to describe the stage at which telomeres are shortened to a critical length such that a proliferative response can no longer be elicited. One of the approaches to prevent or delay the generation of senescent CD8⁺ T cells is based on the well-documented link between telomere shortening and overall replicative potential and function of T lymphocytes. Although telomerase is capable of elongating telomeres and is upregulated in concert with T cell activation, the activity of this enzyme is completely turned off in CD8⁺ T cells that are chronically stimulated in cell culture. One suggested way to improve age-dependent decline of immune function would be to elicit strong cellular immunity by compounds that favour telomerase activity (McElhaney & Effros, 2009).

Other “genetic” factors have also been implicated in the process of immunosenescence. For example, IL-6 gene may be involved in the genetic regulation of longevity. IL-6 VNTR D/D genotypes were associated with increased levels in the blood and brain from Alzheimer’s disease patients and IL6 VNTR allele B could be detrimental for reaching extreme longevity (Capurso et al., 2007; Krabbe et al., 2004). It was also reported that -1082 IL-10 promoter polymorphism was increased in male centenarians as compared to younger men and this genotype was associated with increased production of IL-10 (Krabbe et al., 2004).

Age is also characterized by hormone changes. It seems that oestrogens can have powerful immunomodulating effects, albeit mainly during stress. *In vitro* studies have shown that oestrogens deficiency leads to reduced IL-2 expression (Ku et al., 2009). Oestrogens seem to have important effects on B cells. A study shows that the percentage of conventional B cells (B-2, CD5⁻ CD20⁺ cells) is significantly lower in late post menopause while B-1 cells (CD5⁺ CD20⁺) remain unchanged. It suggests that oestrogens may be involved in maintaining peripheral B-2 cell pool in women. Even if oestrogens seem to influence B cells, hormone replacement therapy does not influence the production of antinuclear antibodies or anti-IL-1 antibodies observed with aging (Kamada et al., 2001). Circulating oestradiol in late postmenopausal women without hormonal replacement therapy is positively correlated to CRP and serum level of IL-6 but the association for IL-6 was not significant anymore after adjustment for other clinical factors. Testosterone levels were also positively correlated with C-reactive protein, TNF α and IL-6 even after adjustment for confounders (Maggio et al., 2011).

Dehydroepiandrosterone (DHEA) has been considered for immunorestitution because serum levels dramatically decrease with age in both sexes. No DHEA-specific receptor has been identified in human T lymphocyte and it exerts probably its action indirectly via

downstream conversion to other steroids, in particular sex steroid. Furthermore, DHEA exerts also anti-glucocorticoid action. *In vitro*, it increases IL-2 production, NK cell activity. Conversely, *in vivo*, it decreases circulating IL-6 levels. However, no consistent *in vivo* data on immune effect of DHEA supplementation in healthy older humans has been reported. Conversely, it shows a beneficial effect for patients treated in the context of systemic lupus erythematosus (Fulop et al., 2007; Arlt & Hewison, 2004). Other studies show that DHEA negatively correlates with basal IL-6 serum levels in older people but this relation is more complex in younger people. DHEA added in culture of PBMCs inhibits IL-6 secretion (Straub et al., 1998; James et al., 1997).

4.2 Comorbidities and medications

The main confounding factor that might impact on immune functions of the geriatric patient is the occurrence of multiple morbidities. These pathologies have potential direct effect on immune cells but the influence of pharmaceutical treatments should also be kept in mind. Recent research has attempted to identify risk factors for mortality and functional decline in older persons. A 7-year community based cohort study shows that 5% of “high functioning” aged individuals display three or four markers of inflammation (IL-6, cholesterol, albumin, CRP). This was associated with a more than 6-fold increased risk of 3-year mortality and a more than 3-fold risk of 7-year mortality independently of other measures of health status (Reuben et al., 2002). This indicates that innate immune parameters are strongly linked to clinical status.

4.2.1 Cardiovascular diseases and associated metabolic disorder

Atherosclerotic plaques contain smooth muscle cells, activated T lymphocytes and monocyte-derived macrophages. Several epidemiological studies have linked systemic low-grade inflammation in older populations to the prevalence and prognosis of cardiovascular disease. High IL-1 β serum levels were associated with congestive heart failure, angina and dyslipidemia. High TNF α serum levels have been correlated with dyslipidemia and a higher prevalence of cardiovascular disease in 80 year olds and with high blood pressure, insulin resistance and common carotid intima media thickness in healthy middle-aged men. IL-6 acts as a marker of subclinical cardiovascular disease in older people and is a predictor of mortality related to cardiovascular disease (Krabbe et al., 2004). TNF α directly causes upregulation of cellular adhesion molecules at the surface of endothelial cells and causes insulin resistance. IL-6 induces procoagulant changes by increasing fibrinogen, tissue factor, factor VIII, von Willebrand factor and platelets. Moreover, both TNF α and IL-6 favour dyslipidemia (Bruunsgaard et al., 2003).

TLRs are expressed throughout the body and are mainly found on professional innate immune cells, including macrophages, dendritic cells and mast cells but also on non-professional immune cells such as endothelial cells and smooth muscle cells. All these cells are present in the atherosclerotic lesion and contribute to the inflammatory response. The expression of several TLRs is increased in atherosclerotic lesions. TLR4 is also increased on circulating monocytes from patients with coronary artery disease compared to controls. Several epidemiologic studies have reported elevated risk of atherosclerosis associated with a large number of infections (Chlamydia pneumonia, Helicobacter pylori, cytomegalovirus (CMV), Epstein-Barr virus (EBV), human immunodeficiency virus (HIV), herpes simplex

virus (HSV) 1 and 2, Hepatitis virus A and B, influenza A virus). Studies have shown that vaccination above the age of 65 decreased the risk of acute coronary syndrome (Nichol et al., 2003; Lundberg & Hansson, 2010). The precise mechanism whereby pathogens are able to accelerate atherosclerosis is unclear but TLRs are probably involved in detection and initiation of a subsequent inflammatory response. TLRs also recognise endogenous ligands that are released during necrotic cell death or are derived from the degradation of extracellular matrix (Heat shock protein, oxidative Low density lipoprotein, endogenous mRNA, fibrinogens,...). While TLR signalling pathways activate the genes encoding IL-1 β and IL-18, these mediators require a second signal resulting in cleavage of the pro-form to release the active molecules. This is regulated by a cytosolic protein complex (the "inflammasome") that leads to caspase-1 activation (Lundberg & Hansson, 2010). Various molecules can activate the inflammasome: ATP, crystalline structures (explaining the role of inflammasome in gout and pseudogout), aluminium salts (used as adjuvants), amyloid-B (playing important role in Alzheimer disease), fibers (silicosis, asbestosis) or the M2 channel from the influenza virus. Cholesterol crystals also directly activate the inflammasome, a process that is implicated in the pathogenesis of atherosclerosis (Duewell et al., 2010; McIntire et al., 2009). It would therefore be of interest to look at inflammasome activation/regulation in the context of aging. Other signalling pathways, such as those linked to the endoplasmic reticulum (ER) stress also participate to inflammation in the context of metabolic disorders (Hotamisligil, 2010). Whether perturbations in ER stress pathways could also contribute to age-related inflammation should also be further investigated (Naidoo, 2009).

Pravastatin, a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors or statin, has been recognize to have beneficial effects on atherosclerosis. Statins have pleiotropic effects, notably on immune system and dendritic cells. It has been shown that patients treated with pravastatin show decreased expression of CD86 on monocyte-derived dendritic cells, a reduced level of IFN α and IL-1 β after four weeks of treatment and an increase of IL-10 and TGF β in mixed lymphocyte reactions. It also reduces plasma levels of inflammation markers (IL-6, TNF α , CRP) and soluble CD40L without apparent link with the degree of lipid lowering achieved (Li et al., 2009; Schonbeck & Libby, 2004). Fenofibrate and simvastatine in type 2 diabetic patients with mixed dyslipidemia and in patients with hypercholesterolemia or impaired fasting glucose, reduce expression of TNF α , IL-1 β , IL-6 and MCP-1 by LPS-stimulated monocytes. Both treatments significantly reduce high-sensitivity CRP levels (Krysiak et al., 2011b; Krysiak et al., 2011a) but there are conflicting results (Coen et al., 2010). Statin and aspirin decrease serum levels of IL-1 β and C-reactive protein in hypercholesterolemic patients (Ferroni et al., 2003). Valsartan in hypertension patients also reduces the secretion of IL-1 β by LPS-stimulated PBMCs. Angiotensin II is identified as the main mediator of vascular complications of hypertension. It stimulates the expression of vascular cell adhesion molecule-1 and induces IL-1 β and MCP-1 production by vascular smooth cells (Li et al., 2005; Ferro et al., 2000).

Type 2 Diabetes mellitus is a serious chronic disease that is very prevalent in the developed world. Several studies have shown that IL-6 and IL-1 β levels are independent predictors of type 2 diabetes development. The role of TNF α is more controversial, some studies show a relationship between TNF α and insulin resistance but this might be restricted to obese type 2 diabetic subjects. Higher serum IL-8 levels have also been found in diabetic patients

(DiPenta et al., 2007). Production of IL-6, IL-8, IL-1 β upon LPS stimulation could also be influenced by glucose concentrations and insulin levels but *in vitro* results on PBMCs do not take into account the contribution of skeletal muscles, fibroblasts and vascular endothelial cells (Beitland et al., 2009).

Chronic heart failure is a major epidemiological burden in the industrialized world. Approximately 2% of the adult population is diagnosed with moderate or severe left ventricular systolic dysfunction with an incidence rate of 10 per 1000 population over the age of 65. Chronic inflammation interacting with increased oxidative stress, cytokine production, proteolytic matrix degradation and autoimmunity is implicated in heart failure pathophysiology by increasing cardiac injury, fibrosis and dysfunction. There are several sources of systemic inflammation in cardiac heart failure (TNF α , IL-1, IL-6, IL-18, MCP-1) due to release from leukocytes and blood platelets as well as the lungs, liver, endothelium and the failing heart itself. These cytokines are capable of modulating cardiovascular performance in an autocrine, paracrine or endocrine fashion. Inflammatory cytokines may enhance the expression of adhesion molecules and inflammatory chemokines in endothelial cells which in turn may further increase the inflammatory response within the vessel wall, representing a pathogenic loop leading to inappropriate endothelial activation in heart failure. TNF superfamily ligands may directly induce endothelial cell apoptosis (Picano et al., 2010). Aged patients with heart failure present higher IL-6 serum levels in the acute but also the recovery phase of cardiac failure compare to healthy aged controls (Vo et al., 2011).

In summary, these “metabolic disorders” are associated with chronic inflammation that contributes to the pathogenesis. Hence, “inflamm-aging” processes are likely to contribute to the development of these pathologies. Conversely, the increased prevalence of these diseases in the geriatric populations will affect innate immune parameters accordingly and favour the maintenance of low-grade inflammation.

4.2.2 The “Frailty” syndrome

Frailty has been defined as an age-related decline in lean body mass, decreased muscle strength, endurance, balance and walking performance, low activity, weight loss accompanied by a high risk of disability, incident falls, hospitalisation and mortality. Plasma levels of TNF α were strongly associated with impendent death independently of dementia and cardiovascular disease in centenarians. It supports the hypothesis that TNF α has specific biological effects and is a marker of the frailty syndrome in the oldest. Systemic low-grade inflammation has been associated with decreased muscle mass as well as the development of functional disability in older population. TNF α might directly contribute to sarcopenia. Indeed, *in vitro* experiments indicate that TNF α disrupts the differentiation process and promotes catabolism in muscle cells. It is also responsible for increased basal energy expenditure, anorexia, loss of muscle and bone mass *in vivo* and has been associated with cachexia in chronic inflammatory disorders such as rheumatoid arthritis, AIDS and cancer. His role in septic shock is well known. The potential role of IL-6 in sarcopenia is less clear. Age-related sarcopenia is partly reversed by exercise. Muscle contractions induce IL-6 production and release into the blood stream and it has been suggested that muscle-derived IL-6 contributes to the beneficial metabolic effect of exercise (Krabbe et al., 2004). Along the same line, another study shows that fatigue resistance and grip work correlate positively with IL-6 in older male participant. In contrast, the same group shows that older nursing

home residents present a worse fatigue resistance and grip work related to high levels of IL-6, Heat shock protein 70 and TNF α (Bautmans et al., 2007; Bautmans et al., 2008). High levels of IL-6, C-reactive protein and TNF α predict an increased incidence of mobility limitation during a 30-month follow-up period in well functioning older people (Penninx et al., 2004).

4.2.3 Neurodegenerative disorders and depression

Cognitive impairment is an important problem with age. Epidemiological studies show an increasing body of evidence on the deleterious association between chronic peripheral cytokine elevation found in aged subjects and cognitive functions. Several studies show an association between serum levels of TNF α , IL-1 β and Alzheimer disease. In contrast, IL-6 seems to be associated with vascular dementia (Krabbe et al., 2004; Ravaglia et al., 2007). Studies have suggested that inflamm-aging can be a prodrome for Alzheimer's disease. Alzheimer's disease is connected with a dysregulation in the metabolism of beta amyloid precursor protein with a consequent transient overproduction or a decreased degradation of β -amyloid in the brain. IFN γ and other pro-inflammatory cytokines interact with processing and production of β -amyloid peptides. Neopterin, a blood compound produced by monocyte-derived macrophages upon stimulation with IFN γ is increased in Alzheimer's disease patients compared to age-matched controls. 70% of these patients are seropositive for cytomegalovirus and it correlates with neopterin and C-reactive protein concentrations. It was suggested that elevated neopterin may be a vestigial result of serum immunity to cytomegalovirus (Giunta et al., 2008). IL-1, IL-6 and TNF α have been clearly involved in the local inflammatory process around amyloid plaques, might be cytotoxic when chronically produced and might stimulate the production of β -amyloid peptides (Krabbe et al., 2004; Ravaglia et al., 2007). As for atherosclerosis, inflammasome activation seems to be implicated in Alzheimer's disease. Amyloid β oligomers can disturb the function of K⁺ channels and decrease intracellular K⁺ concentration leading to activation of NALP-1 then caspase-1, production of IL-1 β and IL-18, and cellular apoptosis through pyroptosis. Fibrillar amyloid β can also lead to the activation of NALP3 and lead to the same phenomenon (Cook et al., 2010). Plasma levels of IL-1 β and TNF α are higher in patients with vascular dementia and late onset Alzheimer's disease when compared to control and after adjustment for confounding variables. IL-6 was only increased in patients with vascular dementia (Krabbe et al., 2004; Ravaglia et al., 2007) but not in Alzheimer's patients (Zuliani et al., 2007). Alzheimer's patients present a decrease of CD8⁺T lymphocytes, a slight increase of CD4⁺ T lymphocytes and CD19⁺ B lymphocytes compared to age-matched controls (Giunta et al., 2008). Once again, there is a strong link between this irreversible neurodegenerative process and general chronic inflammation.

Depression is also a cardinal feature of the geriatric population. Comorbidities, such as cardiovascular diseases, atherosclerosis, diabetes, osteoporosis, dementia, cancer or frailty can precipitate depressive states that are further enhanced by poor socioeconomic outcomes. Depression is a risk factor for low resistance to infection and insufficient response to vaccine. The pathogenesis and severity of depression are connected to chronic stress. Chronic diseases, stressful life events, personal loss, decline in self concepts of efficacy may contribute to this process. Depression in older people is associated with increased exposure to cytomegalovirus in the past and a pro-inflammatory profile demonstrated by elevated

TNF α , IL-6, IFN α , C-reactive protein and deficiency of suppressive IL-10+cells. These changes negatively affect humoral and innate responses in depressed patients (Penninx et al., 2003; Bouhuys et al., 2004; Trzonkowski et al., 2004; Irwin & Miller, 2007). IL-6 and TNF α have the capacity to exert direct effects on the central nervous system by stimulating the hypothalamic-pituitary axis activity and the release of corticotrophin-releasing factor. These direct effects may lead to behavioural and neurochemical changes that may induce depression (Penninx et al., 2003). Depression has been associated with a decreased number of lymphocytes and NK and altered functions, which can be modulated by antidepressant treatment (Bouhuys et al., 2004; Irwin & Miller, 2007). Antidepressant therapy decreases LPS-induced IL-1 β and IL-6 in whole blood from depressed patients. IL-1 β has been shown to up-regulate hippocampus expression of serotonin transporters and proinflammatory cytokines might play a causative role in the depression-related activation of hypothalamic-pituitary-adrenal system (Himmerich et al., 2010).

4.2.4 Osteoporosis

Postmenopausal osteoporosis is a progressive disorder characterized by a decreased bone mass and increased susceptibility to fractures. It affects one out of three women after menopause (Breuil et al., 2010). Oestrogen deficiency leads to an uncoupling between activity of bone resorbing cells (osteoclasts) and bone forming cells (osteoblasts) responsible for accelerated bone loss. The concept of osteoimmunology recently emerged from increasing evidence of intimate links between bone tissue and the immune system. Indeed, recent studies have suggested that the increase in bone resorption induced by oestrogen deficiency is at least partly mediated by increased paracrine production of bone resorbing cytokines (Breuil et al., 2010). Multiple soluble mediators of immune cell function, including cytokines, chemokines and growth factors also regulate osteoblast and osteoclast activity. This is particularly true in pathological conditions such as rheumatoid arthritis and inflammatory bowel disease (Breuil et al., 2010). IL-1 is one of the most potent stimulators of bone resorption and IL-6 appears to be a potent osteotrophic factor that may play an important role in diseases characterized by increased bone resorption. Oestrogens inhibit IL-6 gene expression (Zheng et al., 1997; De Martinis et al., 2006). TNF α and IL-1 enhance bone resorption by stimulating development of osteoclast progenitors and increasing the activity of mature cells. IFN γ inhibits the process of IL-1 stimulated bone resorption. Some studies do not find any differences in the serum levels of IL-1 β , IL-1 α and IL-6 between osteoporotic and normal women. In contrast, IL-1 β , IL-6, TNF α are significantly higher in whole blood after polyclonal activation in osteoporotic women than controls and negative correlation is found between lumbar bone mineral density and IL-1 β , IL-6 or TNF α levels (De Martinis et al., 2005; Zheng et al., 1997). A study performed on osteoporotic women and controls without oestrogen or vitamin D deficiencies shows that osteoporotic women present a decrease in circulating B cells, decreased basal secretion of IFN γ by CD4+ T lymphocytes, a decreased in memory CD4+ T cells expressing RANK+ and CD28+ (Breuil et al., 2010). The TNF-family RANK-L and its receptor RANK are key regulator and essential for the development and activation of osteoclasts. RANK-L is expressed in osteoblasts and can be upregulated by bone resorbing factors such as glucocorticoids, 1,25(OH)2D3, IL-1, IL-6, IL-17, TNF α , PGE2, parathyroid hormone. RANK-L is produced by activated T cells and can directly induce osteoclastogenesis. Several factors can inhibit RANK-L such as osteoprotegerin, IFN γ , IL-12 and IL-18 (De Martinis et al., 2006).

Biphosphonates are currently widely used for the prevention and treatment of osteoporosis as well skeletal metastasis. It has been recently demonstrated that biphosphonates lead to the expansion and activation of $\gamma\delta$ T cells, these effects may represent potential novel anti-tumor mechanisms. Another study indicates that low dose zoledronate *in vitro* reduces TNF α production by monocytes, inhibits upregulation of typical maturation markers and NF κ B activation in dendritic cells (CD83, CD86, CD40) (Wolf et al., 2006).

4.3 Chronic infections and immune “exhaustion”?

One of the hallmarks of the “immune risk phenotype” (see table 1) in the OCTA/NONA subjects is the accumulation of terminally-differentiated CD8 T cells, (lacking CD27 and CD28) leading to inversion of the CD4:CD8 ratio. An important fraction of these cells are specific for cytomegalovirus (CMV) antigens. These effector memory T cells contain large amount of cytotoxic effector molecules like granzyme and perforin and progressively acquire inhibitory receptors such as KLRG1, CD57 and PD-1 (Pawelec & Derhovanessian, 2011). Similarly, CMV-specific CD4 T cells are highly differentiated, have shorter telomeres and decreased telomerase induction after stimulation. These cells are thought to become dysfunctional and “exhausted” in old individuals (Hadrup et al., 2006). However, these cells are still capable of rapidly producing cytokines upon *in vitro* stimulation and display effector functions (Ouyang et al., 2003). Interestingly, a study performed on individuals genetically enriched for longevity, with a 30% decreased mortality risk, possess immune signatures different from those of the general population. Even if they are CMV-seropositive, they fail to show the CMV-(and age-) associated alterations of immune parameters that CMV-seropositive general population does show (Derhovanessian et al., 2010). As previously mentioned, it has been reported that IL-4 producing T cells with a CD25+ memory phenotype accumulate in a subgroup of healthy elderly people who have an intact humoral immune response after influenza vaccination. These apparently beneficial CD8+ CD25+ T cells are rare or even absent in older persons with latent CMV infection (Herndler-Brandstetter et al., 2005).

Could there be a direct link between this CMV-dependent immune signature and other parameters of immunosenescence? Conceptually, accumulation of these memory oligoclonal cells with age would occupy the “immunological space” and limit homeostatic proliferation of naïve T cells and response to new antigens. It has also been suggested that CMV infection could participate to the inflamm-aging process (Trzonkowski, 2003). Whether accumulation of CMV-specific T cells with age is actually detrimental remains to be established (Wills, 2011). Analysis of several recent cohorts does not support a relationship between CMV status, mortality or inflammatory markers (Wills 2011). Another recent study found a gradual increase in CMV antibody titers with deteriorating functional status in aged individuals (Moro-Garcia et al., 2011). CMV infection is also associated with atherosclerosis and the risk for heart diseases (Stranberg TE 2009). In longitudinal studies of CMV-seropositive patients, antibody levels have been reported to correlate inversely with survival in individuals with stable cardiovascular diseases, cardiovascular risk factors and in older women in their 70's. Furthermore, telomere shortening of CD8 CD28- T cells correlates with cardiac dysfunction in CMV+ patients with coronary heart diseases (Spyridopoulos et al., 2009).

In addition to these unresolved issues related to the association of CMV infection and disease states, the causality links are still unclear. Indeed, if CMV infection were directly implicated in age-dependent deterioration of immune functions and cardiovascular diseases, it would be highly beneficial to consider CMV eradication in the general population through vaccination (Pawelec, 2011).

4.4 How living habits and nutrition status impact on immune functions

Malnutrition is associated with a decrease in immunity and an increase in susceptibility to many infectious diseases, notably due to an inability to meet the energy demands associated with the immune response. Interventions on nutrition could have a large impact on immune functions (Ongradi & Kovesdi, 2010).

It seems that caloric restriction is the only known method to prolong median as well as maximal lifespan in all tested animals, from invertebrates to rodents and non-human primates. It is able to attenuate the natural shift from naive to memory phenotype T cells and maintain a higher number of naive T cells in aged animals. The increase of proinflammatory cytokines such as IL-6, TNF α and IFN γ can be reversed by caloric restriction. Caloric restriction is known to inhibit mTOR and thereby promoting autophagy mechanisms. It allows recycling of the cellular components to gain new building blocks for critical proteins by degrading momentarily unneeded proteins and even organelles (Arnold et al., 2011).

The dietary intake of essential macro and micronutrients is usually inadequate in the elderly and several factors contribute to this deficiency: poor socioeconomic status may lead to a greater consumption of inexpensive foods poor in micronutrients. Nutrient deficiency is exacerbated by loss of appetite, lack of teeth, intestinal malabsorption and decreased energy requirement. Many micronutrients contribute directly or indirectly to the biological activity of some antioxidant enzymes, to the efficiency of immune response and to the maintenance of metabolic functions (Mocchegiani et al., 2011).

Vitamin A contributes to the maintenance of epithelium integrity in the respiratory and gastrointestinal tracts. Pyridoxins, folic acid, vitamin E have been suggested to influence lymphocyte functions. Antioxidant vitamin supplements have been shown to enhance antibody titers upon influenza vaccination and to reduce incidence of infection over a 2-year study period (Lesourd, 2006).

Lipids are also important actors in immune system. High-density lipoprotein (HDL) has anti-inflammatory and anti-oxidative effects and influence proximal T cell signalling. Conjugated linoleic acid has been shown to have anticarcinogenic, antiatherogenic and antidiabetic properties correlating with increased lymphocyte proliferation and decreased proinflammatory cytokine secretion. The most important effect is a decrease of risk and severity of cardiovascular diseases originating from atherosclerosis, a chronic inflammatory condition. Living habits can serve as anti-aging process: aerobic exercise, weight loss and smoking cessation can raise HDL levels and physical activity tends to lower IL-6 and C-reactive protein serum levels (Fulop et al., 2007; Ongradi & Kovesdi, 2010).

The potential role for vitamin D and its active metabolite 1,25(OH) $_2$ vitD in modulating the immune response was first appreciated 25 years ago with three important discoveries: The

ability of 1,25(OH)₂vit D to inhibit T cell proliferation, the ability of disease-activated macrophages to produce 1,25 (OH)₂vitD and the presence of vitamin D receptor in activated human inflammatory cells. 1,25(OH)₂vitD suppresses proliferation and immunoglobulin production and delays the differentiation of B cell precursors into plasma cells. It shifts the balance to a Th2 cell phenotype and increased CD4/CD25 regulatory T cells. It inhibits Th17 development and appears beneficial for autoimmunity diseases. In innate immunity, vitamin D enhances activation of TLRs. It promotes innate immune responses to TLR activation by Mycobacterium tuberculosis. 1,25(OH)₂vit D increases cathelicidin, a antimicrobial peptide after activation of TLR1/2 but inhibits the maturation of monocyte-derived dendritic cells (Bikle, 2009; Hewison, 2010; Schwalfenberg, 2011). By increasing cathelicidin, vitamin D supplementation improves the outcome of many diseases: it reduced dental caries and Helicobacter pylori infections. Vitamin D insufficiency is associated with Crohn's disease, poor outcome in severe pneumonia and urinary tract infections (Schwalfenberg, 2011). Vitamin D improves physical barrier by stimulating gap junction genes, adherent genes and tight junction genes (Schwalfenberg, 2011). In contrast, a study failed to show influence of a short-term calcium and vitamin D treatment in healthy post menopausal woman on IL-6, TNF α and C-reactive protein serum levels (Gannage-Yared et al., 2003).

Vitamin C is an essential watersoluble nutrient, which primarily exerts its effect on host defence mechanisms and immune homeostasis, by being the most important physiological antioxidant. It has been implicated as having a preventative and therapeutic role in a variety of diseases including scurvy, viral infections and common cold, cancer and atherosclerosis. A study shows that *in vitro*, vitamin C inhibits IL-6 and TNF α production by monocytes after LPS stimulation and an inhibition of IL-2 production by lymphocytes after PMA ionomycin (Hartel et al., 2004).

Zinc is one of the most relevant nutritional factors in aging because it affects immune responses, metabolic harmony and antioxidant activity. The human body contains 2-3 g zinc most of which is bound to proteins. Plasma pool, which is required for the distribution of zinc represents less than one percent of the total body content. A multitude of factors is likely to influence zinc intake: malnutrition, socioeconomic factors, decreased intestinal absorption and medications like diuretics. The recommended daily allowance for zinc in adult in the United States is 11mg/day for men and 8 mg/day for women. In human, the most prominent example of the effect of zinc deficiency on the immune system is acrodermatitis enteropathica, a rare autosomal recessive inheritable disease that causes thymic atrophy and a high susceptibility to bacterial, fungal and viral infections. It is caused by zinc-specific malabsorption. The intracellular concentration of free zinc is regulated by three mechanisms: one is transport through the plasma membrane; another involves storage in zincosomes and finally zinc binding to metallothionein. Metallothioneins are a group of low molecular weight metal binding proteins with high affinity for zinc. It distributes intracellular zinc and has a protective role in transient and acute stress-like conditions. Elevated IL-6 levels observed in aged individual are also associated with increased and persistent metallothioneins expression in peripheral mononuclear cells, leading to an increased sequestration of zinc and immune impairment. Notably, centenarians display low levels of metallothioneins coupled with satisfactory zinc ion availability. *In vitro* studies show that many parameters are affected by zinc: caspases, reactive oxygen species production, NF κ B and iNOS activity, superoxide dismutase, catalase, glutathione

peroxidase, telomere length, several cytokines and chemokines expression. The most prominent effect of zinc deficiency is a decline in T cell function, the shift of a Th1 toward Th2 responses. Effect of zinc on cytokine levels is concentration-dependent: it stimulates cytokine production in monocytes in response to lipopolysaccharide with moderated supplementation but higher concentrations can have an antagonistic effect. With regard to older people, inconsistent data exist on the beneficial effect of zinc supplementation upon the immune efficiency due to different doses and duration of treatment. The most important parameter affected by physiological dose (10-25 mg/day from 1 to 3 months) is the innate immunity represented by the natural killer cell cytotoxicity. Zinc treatment at the dose of 15mg a day for 1 month in older people and old infected patients restores thymic endocrine activity, lymphocyte mitogen proliferative response, CD4+ T cell number, peripheral immune efficiency and DNA repair. At clinical level, significant reduction of relapsing infections occurs in these patients (Mocchegiani et al., 2011; Haase & Rink, 2009; Mocchegiani, 2010). In hospitalized geriatric patients, poor zinc status has been associated with higher proportion of congestive cardiopathy, respiratory infections, gastrointestinal diseases and depression (Peppersack et al., 2001).

Protein energy malnutrition is common in elderly population. It is present in 2-4% of home-living self-sufficient older subjects and in more than 50% of institutionalized older subjects. During stress, the body reacts with acute phase responses associated with proinflammatory cytokine release from monocytes-macrophages. The cytokines induce the use of nutritional reserves which is particularly harmful in the older people for several reasons: 1) body reserves are already decreased in older individuals who exhibit osteoporosis and often sarcopenia 2) acute phase responses are long lasting in older people, so that more body reserves are used ; 3) nutritional reserves are never fully replaced in older individuals during recovery, since protein anabolism is decreased; 4) each acute phase response in the older people can therefore leads to lower nutritional reserves, mainly muscle protein reserves which can increase frailty (Lesourd, 2006).

In light of these observations, it is clear that addressing the specific nutritional requirements in advancing age could modulate immune functions. Whey proteins are a mixture of globular proteins isolated from milk. It is left when milk coagulates and contains everything that is soluble in milk. It has been shown that older people receiving whey proteins, in comparison to soy proteins, present greater antibody responses against four serotypes of *S. pneumoniae* (Freeman et al., 2010). Along the same line, Enprocal, a recently formulated supplementary food has been designed to meet the nutritional needs of frail older people. The ingredients of Enprocal are dairy-based proteins (Whey protein concentrate, skim milk powder, whole milk powder), vitamins and minerals (calcium, zinc, vitamins C, D, B and A), vegetable oils and inulin. An *in vitro* study suggested that Enprocal displays some immunomodulatory properties on immune cells (Kanwar & Kanwar, 2009). Lactoferrine has also important immune modulator protein. It belongs to the transferrin family and bind two irons ions reversibly. It is synthesized by glandular epithelia and found in milk, tears, bile, respiratory and gastrointestinal secretions. Protein antigens and bacteria within the digestive systems act as stimulating agents in the process. It has pleiotropic effects: bactericidal, anti-fungal and anti-viral effects, anti-oxidant activity, it reduces the production of proinflammatory cytokines, inhibits tumour growth by inhibiting angiogenesis, promoting apoptosis and finally, it promotes bone growth (Pierce et al., 2009).

Exercise has also been shown to have influence on immunological parameter. Studies have found that mitogen- or influenza- induced lymphocyte proliferation was increased, the number of natural killer cells was greater, antibody IgM and IgG response to influenza vaccine two weeks post immunization was greater in active old people. Greater levels of physical activity in terms of walking speed was also associated with lower serum levels of several inflammatory markers such as IL-6, TNF α , and C-reactive protein. In contrast, intervention trials involving frail older people were not promising suggesting that immune alterations in the frail state cannot be reversed (Senchina & Kohut, 2007). A study performed on older men shows that older people with long-term training present reduce levels of IL-6, IL-1ra, IL-10, sTNFRI but an increase of MCP-1 compared to sedentary older people. It was associated with increases of DHEA and IGF-1 levels (Gonzalo-Calvo et al., 2011). Another study shows also that exercise reduces inflammatory monocytes in hypercholesterolemic patients (Coen et al., 2010).

In summary, many different dietary factors are able to influence innate and adaptive immune parameters. It is very difficult from *in vitro* studies to draw hypothesis on how deficiency/supplementation of specific factors impact on the organism. However, clinical studies indicate that these factors should be taken into account and might be beneficial for healthy aging as a whole.

4.5 Erosion of epithelial barriers: susceptibility to infections and potential impact on chronic inflammatory status

Epithelial cells represent the first protective barrier towards invading pathogens. Aging is associated with alteration of these barriers, including the skin, lung, stomach, intestine and urinary tract. Bacteriemic pneumococcal pneumonia in persons older than 70 is associated with a death rate greater than 50 percent. It appears that oropharyngeal colonization with gram-negative bacilli plays an important predisposition role. With age, in the lung, there is a reduced function of the mucociliary tract, a reduced local immunity (T cells and reduced secreted immunoglobulin), and reduced cough reflex. All these factors but also deglutition trouble, reduced production of gastric acid secretion, antibiotics or antacid treatment, favour the apparition of pneumonia in older people (Cretel et al., 2010; Yoshikawa, 1981).

Older people also present more urinary infections than young people. Urinary tract infection has an incidence of 5-35% in men and 15-50% in women. Poor emptying of the urinary bladder because of reduced muscle tonicity, prostatic hypertrophy, reduced oestrogen and increased pH level that lead to increased bacterial adherence, previous genitorurinary instrumentation and perineal contamination from fecal incontinence are possible reasons for the high incidence (Yoshikawa, 1981; Cretel et al., 2010).

Skin and soft tissue infection is a common complication in aged patients. Even minor trauma to the skin might result in serious skin and soft tissue infections because of skin changes (thinning of epidermis and subcutaneous tissues, decreased glandular secretions and atherosclerosis, pressure injuries). Skin also presents modifications of immune cells such as a decrease of Langerhan's cells (Cretel et al., 2010; Desai et al., 2010; Grewe, 2001; Yoshikawa, 1981).

Older patients are also at higher risk for bacterial meningitis (pneumococci, gram negative bacilli and listeria monocytogenes) and bacterial arthritis (Yoshikawa, 1981).

Gram-negative bacterial infections occur more frequently in patients older than 60 years. Intra-abdominal sepsis is of special importance to the older people. Complications like perforation, wound infection, abscess formation and pneumonia are more common in the older people following appendectomies. The risk of diverticulitis rapidly increases with aging and cholelithiasis is another disease of the aged.

With age, the capacity of the gastrointestinal tract to protect individuals from pathogens is lowered because of reduced gastric pH leading to pneumonia and malabsorption, mechanical trouble like diverticulitis and alteration of the mucosal immune system (Cretel et al., 2010). The mucosal immune system consists of an integrated network of tissues, lymphoid and mucous membrane-associated cells and innate effectors and acquired molecules. The IgA isotype is key players in mucosal immunity and seems to function in synergy with innate immune system. Mucosal inductive sites include the Peyer's patches; gut associated lymphoreticular tissues (GALT), Waldeyer's ring of tonsil and adenoid. The mammalian lower intestine contains up to 10^{12} bacteria per gram of intestine. The normal microbiota is essential to maintain appropriate homeostatic conditions providing energy in the form of short chain fatty acids and nutrients and protection against colonization by pathogenic bacteriae. It also plays a role in maturation of the host immune system including intestinal secretory soluble IgA and intraepithelial lymphocyte development. There is some evidence in mice that there are alterations of the mucosal immune system with age. Reduced levels and quality of soluble IgA and alterations of mucosal dendritic cells functions have been reported. Qualitative change in the composition of the microbiota has also been reported (fewer total anaerobes bacteroides and bifidobacterium and higher levels of enterobacteriaceae and endotoxin-producing, gram-negative bacteria like fusobacteria, clostridia, eubacteria species). As a direct result of these age-related changes in the microbiota, the quality of the secretory IgA response can be altered, although the absolute amount of these antibodies is generally unchanged (Fujihashi & Kiyono, 2009). Non-pathogenic bacteriae in the intestine play important role for protecting host from pathogens. It has been suggested that limited TLR stimulation will contribute to the physiological, low-level inflammation in healthy intestine. In contrast, true pathogens induce a rapid and more aggressive response that is initiated by microbial danger signals and tissue damage. It is now known that the innate and adaptive immune activation by the microbiota prevents other inflammatory responses and induces cytoprotective responses of the intestine epithelium that are critical for intestinal homeostasis. This is achieved by low expression of pattern recognition receptors on intestinal epithelial cells and limited gene activation via NF- κ B. It promotes epithelial integrity through production of cytoprotective molecules such as heat shock proteins. Low-grade bowel inflammation is frequently present in the older population and may account for elevated systemic C-reactive protein and faecal calprotectin. Blood intestinal perfusions and oxygenation are also altered in the aged population. It is possible that the combination of a normally harmless bacterial signal, tissue injury and nutritional deficiency may trigger pathogenic inflammatory response. In the intestinal environment, a loss of barrier integrity may result in heightened exposure to exogenous components derived from the non-pathogenic intestinal microbiota and a breakdown in tolerance mechanisms. Impaired clearance of apoptotic cells by intestinal dendritic cells may lead to the accumulation of necrotic cells that release autoantigens such as nucleic acids, uric acid and the induction of an inflammatory dendritic cells phenotype. This might lead to autoimmune response and abnormal immune response to commensals.

Taken together, it seems that both endogenous signals (cell senescence and cumulative cell damage) and exogenous non-self signals (bacteria translocation through a leaky gut) may both contribute to chronic inflammation (Schiffrin et al., 2010).

5. Immunosenescence and cancer

Epidemiological studies indicate that about 55% of tumours are detected after the age of 65. The most frequent sites in men over 65 are represented by lung, colon, rectum, prostate and bladder; in women by breast, lung, colon-rectum, bladder and pancreas as well as non-Hodgkin lymphoma. The association between age and cancer can be explained by a multitude of factors, including a more prolonged exposure to carcinogens in older individuals and an increasingly favourable milieu for the induction of neoplasm in senescent cells. The immune system counteracts tumour cell growth through different ways:

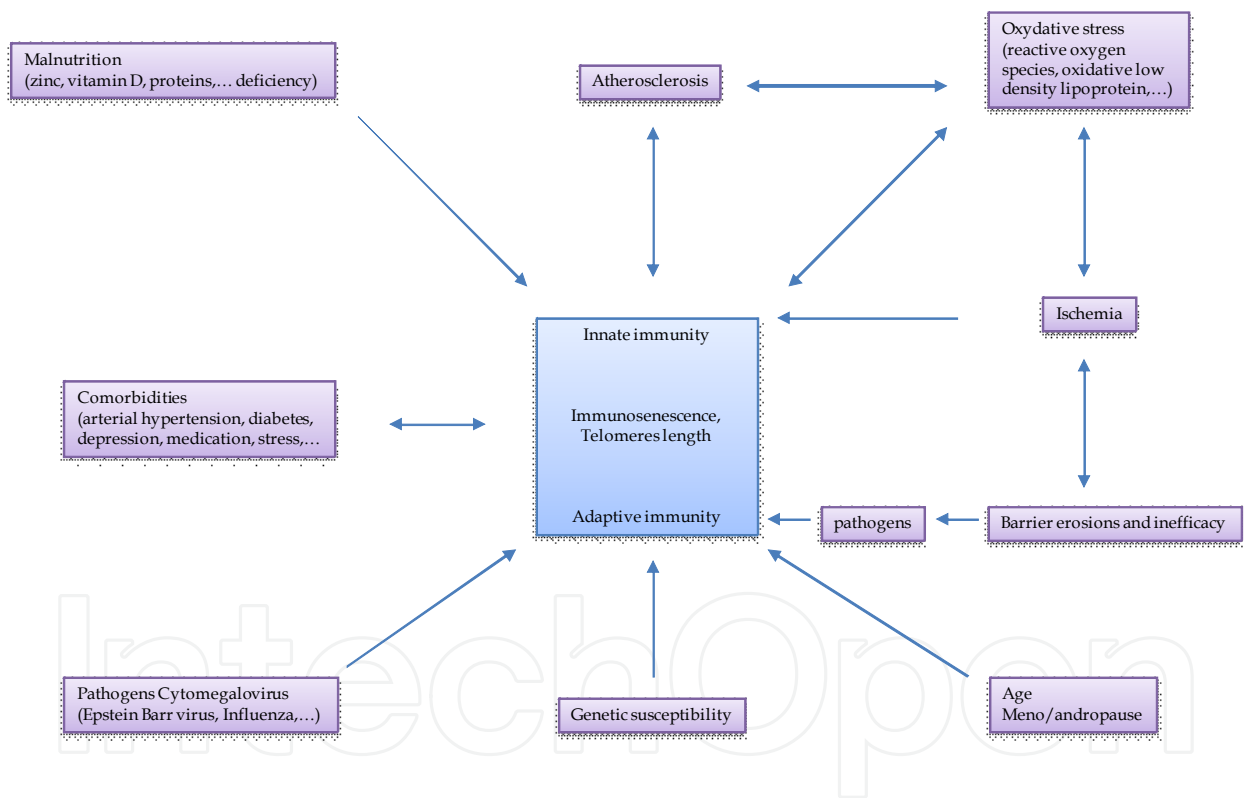


Fig. 7. External factors leading to immunosenescence.

1) protection of the host from virus-induced tumours by eliminating or suppressing viral infections 2) suitable eradication of pathogens and rapid resolution of inflammation thereby preventing the establishment of an inflammatory environment favourable to tumorigenesis 3) specific identification and elimination of tumour cells on the basis of their expression of tumour-specific antigens or molecules induced by cellular stress (a process known as “immunosurveillance”). Hence, reduction of T cell function and cellular immunity as seen in the older people could favour carcinoma development. In older people suffering from different types of cancer, there was a reduced number of CD3 T cells, CD4 T helper cells and

natural killer cells in peripheral blood compared to healthy older people (Malaguarnera et al., 2010; Fulop et al., 2010; Motta et al., 2003). "Inflamm-aging" processes could favour tumour development. For example, IL-1 α plays a role in tumorigenesis (and promotes angiogenesis and chemoresistance). TNF α plays an important role in the initiation of tumour by stimulation the production of nitric oxide and reactive oxygen species which can lead to DNA damage. Enhanced TNF α levels are associated with increased risk of multiple myeloma, hepatocellular carcinoma, bladder, gastric and breast cancer. It also correlates with poor prognosis of haematological malignancies. The paracrine secretion of IL-6 acts as a growth factor for multiple myeloma, non-Hodgkin lymphoma, bladder, colorectal and renal cell carcinoma (Malaguarnera et al., 2010; Fulop et al., 2010).

Accumulation of memory CD8 T cells might also participate to cancer development. One of the most intriguing evidences about the role of CD57+ T lymphocytes in cancer comes from the fact that metastasis-free regional lymph nodes draining different human epithelial tumors present a reduction in almost all immune cells, except CD57+ lymphocytes (Kanwar & Kanwar, 2009). CD8+CD28-CD57+ T lymphocyte clones may be the result of persistent stimulation by tumor-associated antigens, combined with a reduced cellular death rate secondary to reduced expression of the apoptosis-related molecule CD95. A long-lived population of CD8+CD57+CD28- perforin+ T lymphocyte clones has been reported in the peripheral blood of patients with multiple myeloma. Despite being more commonly found in patients with progressive and advanced-stage disease, this population was associated with superior survival. In patients with relapsed/refractory multiple myeloma treated with thalidomide, multivariate analysis showed that inferior survival was associated with low pretreatment bone marrow CD57+ cells and overall, CD8+CD57+T lymphocytes account for up to 25% of the marrow T cell population. Such CD8+CD57+ T lymphocytes have been shown to suppress T cell functions in multiple myeloma (Focosi et al., 2010).

CD57+ lymphocytes in the lymph nodes of B-chronic lymphoid leukemia patients have abnormal orthogonal light-scattering signals and an abnormal density of CD57+ receptors in comparison with their peripheral blood CD57+lymphocytes or the CD57+ lymphocytes in the peripheral blood, bone marrow, and tonsils of hematological normal donors. It has been reported that these patients with neutropenia have higher numbers of peripheral blood CD8+CD57+ T lymphocytes than the non-neutropenic ones. An elevated frequency of CD4+CD57+ T cells was correlated with more advanced disease. The role of the CD4+perforin+ T cell population is at present uncertain. However, this potentially cytotoxic T cell population could contribute to enhancing survival of the B-chronic lymphoid leukemia cells through production of IL-4 and to the immunodeficient state seen frequently in patients with this tumor, independent of drug treatment. (Focosi et al., 2010).

Finally, few reports analyzed the impact of immunosenescence on the complications of patients with cancer. Neutropenia is a complication of patients treated by chemotherapy and responsible of infection called febrile neutropenia. In older patients, pyrexia can be absent and little is known about the consequence of neutrophil defect and other immune defects on the increased rate of infections in old cancer patients. It is well known that CSFs enhance bone marrow production and is used to counteract neutropenia. CSFs have proven to be beneficial in old people but they still suffer from increased infection rates compared to younger adults. Finally, the factors influencing immunity (such as malnutrition, alteration of intestinal barriers, depression...) can also negatively influence the outcome of cancer in

geriatric patients. So, it will be important to reconsider guidelines and management of old patients suffering from cancer (Crichton & Puppione, 2006).

6. Immunosenescence and autoimmunity

“Inflamm-aging” results in both decreased immunity to exogenous antigens and increased autoreactivity. It is well documented that a significant fraction of older people has low affinity autoantibodies in their serum and the prevalence of autoantibodies associated with autoimmune disease increases with age without clinical significance. Rheumatoid factors are present in up to 5% of young healthy individuals and increase up to five times in older persons such as antinuclear antibodies. A number of hypotheses have been proposed to explain the relationship between aging and the development of autoimmunity: reduced thymic output has been postulated to induce compensatory autoprolieration of T cells which can lead to premature T cell senescence and contribute to autoimmunity; alteration in apoptosis in T cells, expansion of exhausted CD4 and CD8 T cells that have lost the expression of CD28 are associated with autoimmune disease like rheumatoid arthritis, reactivation of self-reactive memory B cells, a shift from Th1 to Th2 cytokine profile that enhances the production of autoreactive antibodies, elevated levels of circulating inflammatory cytokines such as IL-6, TNF α and C-reactive protein is related to age-related diseases such as coronary heart disease and stroke, diabetes mellitus, Alzheimer’s disease, lupus, Sjogren’s syndrome and rheumatoid arthritis (Grolleau-Julius et al., 2010).

7. Immunosenescence and vaccination

Influenza is the fifth leading cause of death in the developed world after 50 years of age. As such, this group is the major target of vaccination campaigns. While influenza vaccination has 70-90% efficacy in healthy adult in western countries, the success rate falls to 17-53% in older people when determined as specific immune responses. Nevertheless, vaccination campaigns in aged individuals result in 25% reduction of morbidity, 50% of pneumopathies, 20% of hospital care and 70% of mortality (Ongradi & Kovesdi, 2010; Gruver et al., 2007; Bouree, 2003; Nichol et al., 2003). Both humoral and cell-mediated influenza specific responses are lower than in young adults. Upon *in vitro* restimulation, peripheral blood mononuclear cells exhibit a decrease in the proportion of IFN γ + T cells. Mortality is associated with coexistent bacterial infection in one third of case, which could be a consequence of altered innate immune responses (Ongradi & Kovesdi, 2010; Gruver et al., 2007; Bouree, 2003). In older people, low plasma level of DHEA, decreased TNF α in whole blood after lipopolysaccharide stimulation and increased IL-10 production in whole blood after PHA stimulation is correlated with lower antibody response to influenza vaccination. The increase of IL-10 is likely to inhibit the maturation of antigen presenting cells, together with decreased TNF α production, hampering their migration to draining lymph node, compromising the subsequent induction of the specific immune response. Furthermore, IL-10 can induce antigen-specific CD4 T cells anergy. Thus, it is intriguing that the possession of an anti-inflammatory genotype (high IL-10 and low TNF α production) is increased significantly in centenarians. It is tempting to speculate that the presence of “high IL-10/low TNF α ” could be favorable in protecting against age-related diseases, particularly neurodegenerative diseases, but conversely it could hamper the immune response to infections and vaccine (Corsini et al., 2006). As said before, studies show a correlation

between the cytomegalovirus seropositive status and non responsiveness to influenza vaccine. They show that majority of volunteers fulfilling the criteria of SENIEUR protocol belonged to responders generating protective titers of antibodies against antigens of the influenza vaccine. Proinflammatory status such as elevated serum IL-6, TNF α was also associated with non-responders. The increase of anti-inflammatory cytokines in non-responders may be seen as a compensation for the inflammatory activity of IL-6 and TNF α . The coexistence of high levels of IL-6 and anti-CMV IgG suggested to the authors that chronic infection may be one of the causes of the proinflammatory status in the non-responding group, shrinking the capacity of immune system (Trzonkowski et al., 2003). Decreased TLR responsiveness of dendritic cell subsets is also associated with the inability to mount protective antibody responses to the trivalent inactivated influenza vaccine currently recommended (Panda et al., 2010).

Infection caused by *Streptococcus pneumonia* account for 25-35% of bacterial pneumonia resulting in hospitalization, morbidities and mortality in the older people. The current pneumococcal polysaccharide vaccine is recommended for all individuals above 65 years of age and those between 18-65 years of age at risk. The data for efficacy in older people are not as persuasive. Antibodies levels are lower in the older people and in those with chronic disease, except for healthy older adults after the age of 75 (modified SENIEUR protocol) (Chen et al., 2009; Bouree, 2003). Antibody concentrations were found to be similar for six out of seven serotypes for streptococcus pneumonia after vaccination of older and young subjects while opsonization titers were significantly higher in six out of seven serotypes in the younger population. Antibody potency, as measured by the ratio of opsonization titer to antibody concentration was found to be significantly higher for the younger subjects for all serotypes. Effectiveness of antibodies seems to be reduced in the older adult population (Schenkein et al., 2008). Tetanus, diphtheria and pertussis vaccination coverage are low, persons aged of more than 60 years frequently do not have protective antibody. It is the same problem for hepatitis B virus vaccine (Chen et al., 2009; Bouree, 2003).

Widely used adjuvant formulations such as those containing alum are poorly effective in older people compared with young subjects (Fulop et al., 2007). Alteration of TLR function in older adults is particularly relevant in view of the increased development and use of TLR agonist in vaccine. Influenza vaccine formulation in clinical trials employs the TLR5 agonist flagellin that would not require yearly reformulation and administration. CpG-containing oligonucleotides are used as TLR9-dependent vaccine adjuvants in the 7-valent pneumococcal conjugate vaccine and significantly enhanced the proportion of vaccine responders amongst HIV-infected adults. MPL, a derivative of lipid A from lipopolysaccharide is already used as an adjuvant in vaccines against human papillomavirus (Cervarix) (Shaw et al., 2011).

8. Conclusion

The first obvious conclusion is that immunosenescence is a complex phenomenon, which does not only reflect the action of time on immune cells. As discussed herein, many other factors, such as genetics, infection history, nutritional status, co-morbidities, socio-economic factors are likely to contribute to this process and its clinical impact. Geriatric medicine has to take into account all these specific characteristics to provide better care to this age group.

Data from literature and our ongoing study tend to suggest that “inflammaging” appears not only with age but is associated with indicators of frailty and the occurrence of comorbidities. Frail geriatric individuals express higher seric levels of TNF α and IL-6. This persistent chronic inflammation could directly participate to dampened innate immune responses upon stimulation. Indeed, *ex vivo* whole blood response to molecules like LPS tends to be reduced in older people. In intensive care units, old people with high basal levels of TNF α and IL-6 show increased severity of sepsis after community-acquired pneumonia (Mira et al., 2008). Intriguingly, increased IL-6 levels in the course of community acquired-pneumonia, is also associated with more severe sepsis. This might reflect the fact that *ex vivo* blood experiments do not take into account cytokine production by stromal cells such as endothelial cells, adipocytes or muscle cells. Moreover, circulating cytokine levels are also influenced by kidney function that is generally altered in the course of sepsis (Gomez CMH, 2000). Finally, it is possible that in the earlier phase of infections, old people are less efficient to control infection, leading to increased late inflammatory response.

Epidemiological associations do not always reflect causality. It is possible to link altered immunological parameters with frailty and comorbidities (fig 3). Should we conclude that dampened immune responses and exacerbated inflammation contribute to the fragility of the organism or that specific pathologies lead to immunosenescence? It is likely that both hypothesis are valid and reinforce each other. It has important implications in terms of therapeutic interventions. Should we treat or prevent chlamydia, CMV or *H. pylori* that could be responsible for local inflammation within atherosclerotic plaques (Rosenfeld & Campbell, 2011)? Would treatment of metabolic disorders reduce “inflammaging” processes? Should we try to “rejuvenate” the immune system through cytokine or hormonal replacement (Dorshkind et al., 2009)? Is the CMV-associated immune phenotype responsible for increased mortality rate or is it possible that frail individuals undergo more frequent reactivation of CMV, leading to the skewing of the memory response? To answer these crucial questions, clear immunological and biological parameters will have to be used is well-defined populations to overcome the weight of confounding factors.

Finally, to improve geriatric health, it seems clear that one should take into account several features of older people. We cannot imagine improving vaccinal responses without correcting nutritional status, frailty, controlling comorbidities and evaluate the impact of drug treatments. So even in this specific field, geriatric medicine requires multidisciplinary approach.

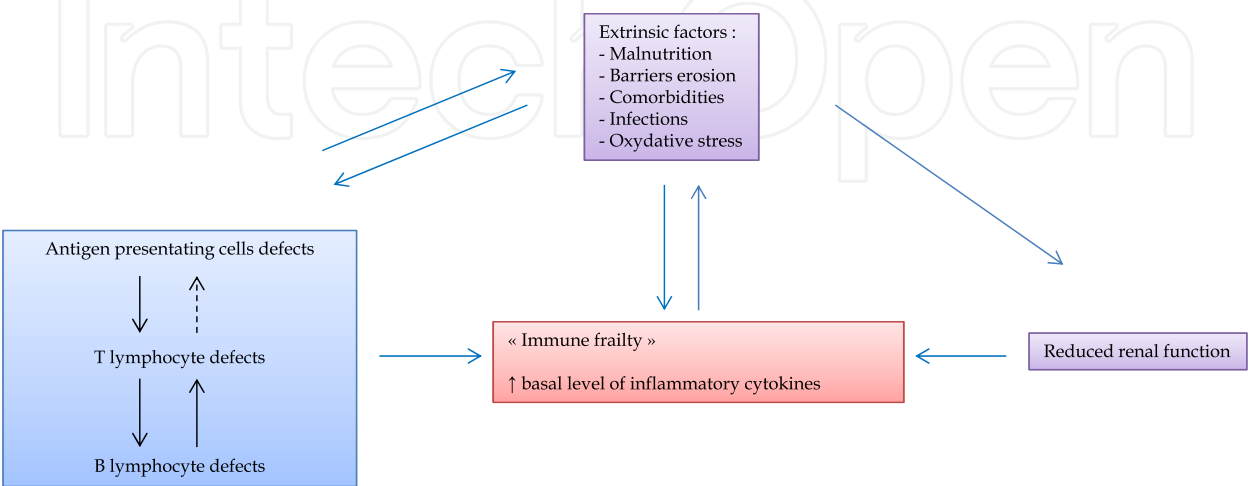


Fig. 8. Potential interplays between immune function and extrinsic factors.

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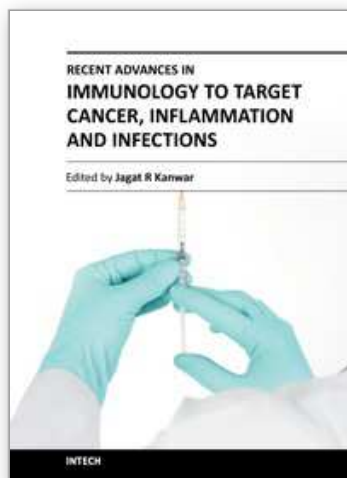
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Immunology is the branch of biomedical sciences to study of the immune system physiology both in healthy and diseased states. Some aspects of autoimmunity draws our attention to the fact that it is not always associated with pathology. For instance, autoimmune reactions are highly useful in clearing off the excess, unwanted or aged tissues from the body. Also, generation of autoimmunity occurs after the exposure to the non-self antigen that is structurally similar to the self, aided by the stimulatory molecules like the cytokines. Thus, a narrow margin differentiates immunity from auto-immunity as already discussed. Hence, finding answers for how the physiologic immunity turns to pathologic autoimmunity always remains a question of intense interest. However, this margin could be cut down only if the physiology of the immune system is better understood. The individual chapters included in this book will cover all the possible aspects of immunology and pathologies associated with it. The authors have taken strenuous effort in elaborating the concepts that are lucid and will be of reader's interest.

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