Review

Aging of the Immune System with High Risk of Disease Progression: A Review

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Abstract

An age related changes dysregulated immune function that contributes to more susceptible infections, having reduced response to vaccines, with increased occurrence of cancer, autoimmune and chronic diseases. Immune responses are influenced by the age-related changes in this system. Immunosenescence is known by a reduction in both cell-mediated and humoral immune responses. These alterations lead to reduced response to vaccines and may be associated with changes in the immune system that are associated to increased susceptibility to diseases. In this review, an effort is made to recapitulate the present knowledge on how the immune system is concerned by the aging progression.

Keywords: Aging, T cell, Immune system, Immunosenescence.

INTRODUCTION

Aging is a natural phenomenon which is a progressive deterioration in the physiologic function that occurs as a consequence of cumulative molecular, cellular and organ damage exhibited by all biological species. At present, there has been an increase in the aging population across the world coupled with declining birth rates and an increased lifespan of individuals. The proportion of the elderly in developing and less developed countries is also expected to increase (Anis et al., 2013). According to WHO, the proportion of old individuals (over the age of 60 years) will rise to 22% of the world population (WHO, 2014). It is estimated that till 2050 the number of older persons in the world will exceed the number of younger persons. Aging of the immune system contribute to the more susceptibility of aged persons to infectious diseases, vaccine failure, cancer, autoimmunity and other chronic diseases (Pawelec, 2013; Targonski et al., 2007)). Immunosenescence affects mainly immune cells, monocytes, natural killer (NK), and dendritic cells (DC), B and T lymphocytes. Immunosenescence is also affected by primary and secondary lymphatic organs like bone marrow, spleen and thymus.

However, innate immunity appears to be better conserved and more harsh; often damaging age-dependent changes which occur in the immune system (Franceschi et al., 2000). Moreover, aged individuals likely present a chronic low grade inflammatory state that has been concerned in the pathogenesis of several age related diseases such as atherosclerosis, Alzheimer’s disease, osteoporosis and diabetes etc. (Griffin, 2006; Pradhan et al., 2000). Though, some individuals turn up to advanced ages without any main health problems, referred to as healthy aging. The immune system dysfunction seems to be someway moderated in this population, probably due to heritable and environmental features yet to be described. This review would only deal with changes that may contribute to documented shortfalls in both innate and adaptive immunity as well as the pathological states and the increased morbidity and mortality seen in the aged population.

Organ Specific Host Resistance

Defence is one of the primary functions of the immune system. It has been noted that with advancement of age there are several functional changes in the host organs.
leading to lowering of defence causing infection of the organs. The combined effects of changes ultimately determine the susceptibility of the individual to infections. Age-related alterations in organ-specific defences are enumerated in Table 1.

Aging of hematopoietic stem cell and lymphoid progenitor cells

Immune cells are frequently renewed from haematopoietic stem cells (HSCs). On the whole capacity for renewal of these stem cells beg to be excused (Lansdorp et al., 1994) and the total amount of haematopoietic tissue in the bone marrow diminish with age (Hartsock et al., 1965). In haematopoietic stem cells (HSCs) changes of the niche as well as variations of hormone production may disturb self-renewal and lineage assurance (Dykstra and de Haan, 2008; Chen, 2004). Human HSCs proliferation correlates inversely with age, possibly resulting from shortening of telomeres (Vaziri et al., 1994). Erythroid and myeloid progenitors are not changed with age. In contrast, there are changes in B cell development. Except in bone marrow, fewer pro-B cells are generated and fewer of these cells transit into subsequent differentiation step, which result in a lower number of mature B cells (Kottner et al., 2013). Bone marrow derived T cell lymphocyte precursors which migrate into thymus seem to be less affected by aging.

The involution of the thymus gland leads to change in the immune system with aging. Thymic involution measured by thymic mass begins at puberty and is almost complete by mid-life. Experimental subsets have shown that there is a shift with age in the proportions of subsets (CD4 and CD8) with in the pool which express CD44+/CD25+/CD57- cell decline with the age (Thoman, 1995).

Age related changes in Innate Immunity

Age-related changes summarised in Table 2.

(i). Skin and mucous barriers:

Skin and mucous membranes constitute the first line of defence against pathogens, with both a barrier and mechanic function; (Castelo-Branco and Soveral, 2014) with age skin cell replacement declines, sweat and sebum production decrease and structural changes such as flattening of the dermo epithelial junctions, depletion of Langerhans cell and melanocytes: dermal and subcutaneous atrophy occurs (Fenske and Conard, 1988; Kurban and Bhawan, 1990; Kottner et al., 2013). With a decreased function of epithelial barriers of the skin, lung or gastrointestinal tract, which facilitates pathogenic organisms to invade mucosal tissues, results in an increased challenge for the aged innate immune system is associated with aging (Gomez et al., 2005; Nomellini et al., 2008).

(ii). Age-Associated changes in Accessory Cells:

With aging neutrophils, monocytes/macrophages and dendritic cells, undergo changes that lead to compromised functioning of the immune system. Defective Toll-like receptor (TLR) function has also been studied in monocytes, where the synthesis of cytokines, IL-6 and TNF-α have been shown to be reduced when induced by TLR1/2 (vanDuin et al., 2007). Production of pre-inflammatory cytokines by monocytes in response to TLR-1/2 ligands ex-vivo is impaired in older adults although whether age affects response to other TLR agonists such as the bacterial endotoxin lipopolysaccharides(LPS_a TLR-4 agonist) remains controversial (Hearps et al., 2012).

Natural Killer cells

Natural killer cells (NK cells) play a function in maintaining innate and adaptive immune responses by secreting a variety of cytokines (Camous et al., 2012; Hazeldine and Lord, 2013). The secretion of cytokines and cell cytotoxicity, mechanisms are carried out by two main sub-populations: CD56dim CD16+ NK cells, which are truly cytotoxic cells with low cytokine production and CD56 bright CD16-NK cells, which are less differentiated cells main response upon activation is cytokine and chemokine production (Fauriat et al., 2010). It has been reported that in the elderly individuals the number of NK cells is increased (Facchini et al., 1987). Cytokine secretion by NK cells also to be reduced (Mariani et al., 1987) as well as variably diminished proliferative response to stimulation with IL-2 (Borrego et al., 1999).

Neutrophils

Neutrophils are short-lived phagocytic cells circulating in blood vessels until they are recruited to site of infection by cytokines and chemokines, mainly IL-1 and IL-8. They are the first responders to microbial and parasitic infections and act by three main mechanisms: phagocytosis, generation of reactive oxygen species and degranulation of microbial peptides. In regard to phagocytosis, most authors agree that the phagocytic function and the intracellular respiratory burst necessary to kill bacteria are reduced in the elderly (Wenis et al., 2000; Emanuelli et al., 1986; Butcher et al., 2001; Fulop et al., 1985; Simell et al., 2011; Fortin et al., 2008). The defect in phagocytosis of opsonized bacteria and superoxide generation seems to depend on a reduced expression of CD16. How age affects the generation of neutrophil extracellular traps remains to be classified (Solana et al., 2012).
Table 1. Age Related changes in Organ Specific Defences

<table>
<thead>
<tr>
<th>Organ</th>
<th>Changes in Defence Mechanism</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Breach in skin integrity due to epidermal and dermal atrophy and decrease in number and function of Langerhan’s cells.</td>
<td>Increased infection.</td>
</tr>
<tr>
<td>GI Tract</td>
<td>Loss of gastric acidity.</td>
<td>Bacterial overgrowth.</td>
</tr>
<tr>
<td>Lungs</td>
<td>Reduced expiratory flow rate and vital capacity; increased residual volume and ineffective alveolar macrophage function.</td>
<td>Diminished clearance of infection.</td>
</tr>
<tr>
<td>Bronchi</td>
<td>Sluggish mucociliary transport.</td>
<td>Diminished clearance of infection.</td>
</tr>
<tr>
<td>Pharynx</td>
<td>Abnormal swallowing mechanism and impaired cough reflux.</td>
<td>Aspiration.</td>
</tr>
<tr>
<td>Kidney</td>
<td>Inability to maintain osmolality, pH and concentrations of organic acid, urea and Tam-Horsfall protein.</td>
<td>Bacterial, bacteriuria and urinary tract infection.</td>
</tr>
<tr>
<td>Bladder</td>
<td></td>
<td>Reflux, ascending infection.</td>
</tr>
</tbody>
</table>

Table 2. Summary of aging changes in innate immunity

<table>
<thead>
<tr>
<th>Component, characteristic</th>
<th>Aging perspective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural killer cells</td>
<td>Increased cell number compensates for impaired function.</td>
</tr>
<tr>
<td>Per cell killing</td>
<td>Impaired, diminished target binding; impaired response to stimulatory cytokines</td>
</tr>
<tr>
<td>Macrophages</td>
<td>Appears intact</td>
</tr>
<tr>
<td>Phagocytosis</td>
<td>Impaired tumor lysis related to impaired response to IFN-γ</td>
</tr>
<tr>
<td>Killing</td>
<td>Decreased cell number</td>
</tr>
<tr>
<td>Langerhan cell</td>
<td>Decreased the capacity to stimulate antigen specific T-cells,</td>
</tr>
<tr>
<td>Dendritic cell</td>
<td>Lymph node homing</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>Decreased bacterial activity and oxidative burst</td>
</tr>
</tbody>
</table>

Macrophages

Macrophages play a role as pathogen sensors and act in important role in the instigation of inflammatory responses, elimination of pathogens, regulation of the adaptive immune response and repair of damaged tissue (van Duin et al., 2007). In older people, macrophages present a reduced production of cytokines such as TNF-α and IL-6 in response TLR1/2 but not other TLR that might be responsible for a less potent recruitment of neutrophils and other cells (van Duin et al., 1990). Reduced levels of MHC class II molecules (Zessel et al., 1999; Plowden et al., 2004) which may contribute to poor CD + T cell responses in aging human and rodent macrophage populations.

Dendritic Cells

In both the innate and adaptive immune system dendritic cells play a critical role in linkage. Yet, it is still not fully understood if dendritic cells are affected by age. In vitro generated DCs, originated from peripheral blood monocytes from elderly persons are functionally intact regarding differentiation and maturation (Steger et al., 1996; Lung et al., 2000).

Status of cytokines

The production and interaction of cytokines produced by cells of innate immunity are very complex. There is a decrease in the levels of IL-2 production by T cells of aged human and mice induced by lectin mitogens (Millar, 1995). The age-dependent decline in IL-2 secretion has been noted to be associated with a parallel decline in IL-2 mRNA production. On the other hand, the production of IL-2 in vitro by T cells of aged humans is remarkably variable (Wu et al., 1986). The age related enhancement in stimulated production of IL-6, IL-8 and TNFα and a decrease in IL-1 production (Pawelec, 1999; Ershler and Keller, 2005). Many researchers have reported that there is an age associated increase in the production of the anti-inflammatory cytokines IL-10 (Castle et al., 1999; 1997). On the other hand, IL-10 production by T-cells from old
mice showed an increase when anti-CD3 is used as a stimulus and a decrease when co-stimuli including IL-2 and or IL-4 are added. (Green-Johnson et al., 1991).

Inflammation in Aging

Inflammation is a strongly regulated mechanism that ensures recruitment of proficient cells and regulation of their functions for the clearance of pathogens. The actors of inflammation are cytokines, chemokines, adipokines, soluble mediators of inflammation and acute phase proteins, among others. An imbalance in this tightly regulated process may lead to significant consequences. In the inflammatory process not only immune cells, but also endothelial cells, fibroblasts and keratinocytes, among other cell types are able to produce these mediators and are partners and players of immune responses.

Inflammation in aging is often referred to as low-grade inflammation (De Martinis et al., 2005). A set of pro-inflammatory mediators in aging such as RANTES, MIP-1α, IL-8, MCP-1, IL-6 and TNFα have been identified. These inflammatory mediators were associated with atherosclerosis, dementia and diabetes amongst other age associated diseases. These markers in high quantities are linked to comorbidities and also to mortality (Bruunsgaard et al., 2003). An important set of markers associated with comorbidities and mortality is IL-6,TNF – α and CRP (French and Harrison, 1984).

Age related changes in adaptive acquired immunity

Age-related changes summarized in Table 3.

Humoral Immunity

There are conflicting reports regarding the age related changes in the concentrations of immunoglobulin isotype in serum. It has been determined that activity of serum poly reactive immunoglobulins changes with age in practically healthy people from the age of twenty five to seventy. The activity of serum IgG increases mostly about 3-4 times (Bobrovnik et al., 2014). While our study has revealed up to five-fold increase with age in serum concentrations of IgM and IgA and all subclasses of IgG in several strains of inbred mice, other study showed no age-associated changes in any of the immunoglobulins except for IgG2a, IgG2b and IgG1. In human, while some showed no changes in immunoglobulin isotypes (Paganelli et al., 1992), others noted a four-fold increase in IgA levels and smaller increase in other isotypes (Armitage et al., 1993), in elderly subjects. It has been noted that aging leads to increase in serum concentrations of self-antigens in human, non-human primates. These autoantibodies found in as many as 80% of elderly individuals are generally of low affinity having no pathological significance (Juby et al., 1994) however, there role in cellular functions in terms of antigens presentation and T cell stimulation has not been worked out.

B Cells

B cells main function is the production of specific antibodies in response to specific antigen and this function is critical and effective in pathogenic infections and vaccination (Gibson et al., 2009). High-affinity-specific antibodies are produced by somatic hypermutation of immunoglobulin genes in the germinal centers of secondary lymphoid tissue after which professional antibody secreting plasma cells migrate to the blood stream (MacLennan, 1994). It has been noted that there is an age related decline in antibody response to B-cell mitogens which require the help of T-cell for antibody production. However, several experiments could not provide such evidence (Weksler and Szabo, 2000). It is further noted that the response of B cells to synthetic hapten which requires T-cell help decline with age. It has been noted that three major impairments affect B-cells with aging. A decrease in number of naive B cells and therefore an impaired capacity of memory B cells that correlates with a lower level of circulating antibodies after contact with a previously known antigen and functionally impaired antibodies with lower affinities and decreased opsonizing abilities (Castelo-Branco and Soveral, 2014).

T cells:

The number and frequency of T cells are variably mentioned to decrease with age; however no clear consensus exist (Anis et al. 2013). T cells are characterized by the presence of T cell receptor (TCRs) and can be categorized in two main subsets by the cell surface expression of either CD4 or CD8. CD4+ cells which distinguish antigens in the context of class II major histocompatibility complex (MHC), are mainly regulatory cells whereas CD8 cells are mainly cytotoxic cells that recognise antigen presented with in class I MHC molecules. Both functions are of vital importance in the adaptive and innate immune response (Castelo-Branco and Soveral, 2014). Thymic involution has been well established in the literature and is considered to be the main mechanism by which the pool of naive T cells decline with age (Moro-Garcia et al., 2012; Ferrando-Martinez, 2009). In spite of thymic involution, a dramatic decline of diversity occurs after the age of 70, a diverse naïve CD4+ T cell compartment is maintained for decades which result in a severely constricted collection (Goronzy and Weyand, 2003). Similar changes in the CD8+ sub population take place even earlier in life (Effros et al., 2003).

In about 80% of healthy elderly individuals, a non-regulatory CD+ CD45RO+ CD25+ T cell population,
which produce IL-2 and displays a highly diverse TCR repertoire, occurs (Herndler-Brandstetter et al., 2005). Phenotypic and functional characteristics is shown with naïve T cells from young persons and persons with a protective humoral immune response to vaccination can still raise a high percentage of CD8+CD25+ cells (Schwaiger et al., 2003). In elderly persons CD8+ CD45 RO +CD25+ cells may reimburse the loss of functional naïve T cells and represent a good biomarker for immunological competence (Herndler-Brandstetter et al., 2008). Approximately 70% of old age individuals lack significant numbers of this specific cell type (Schwaiger et al., 2003). CD8+ CD45 RO+ CD25+ T cells could be propagated by in vitro expression is still imaginable. The resulting population could then be stored and re-transferred in case of immune deficiency, such as after immunosuppressive or radiation therapy (van Duin et al., 2007). The proportions of memory T cells (CD44) have been found to increase with age in the blood, spleen and peripheral lymph nodes of both CD4 and CD8 pools in mice (Flurkey et al., 1986). Expression of another marker of CD4 naïve cells, 3G11, also declines with age.

CD28 is an important co-stimulatory molecule present in T cells and the binding of CD28 to its co-receptor (B7, in antigen presenting cells) results in potent activation stimuli for T cells (Finney et al., 2004). CD28 presence in T cells decreases with cell differentiation from naïve to central memory to effectors memory cells as a result of persistent antigenic stimulation and proliferation cycles (Vallejo, 2005). The activation of T cells via TCR-CD28 does not seem to be impaired in old people (Sansoni et al., 1997). However, with age, CD28 expression decreases in both CD4+ and CD8+ T cells (Weyand et al., 1998; Nociari et al., 1999), consistent with a decreased naïve cell pool and the accumulation of highly differentiated T cells. CD27, and TNF–α receptor, suffers the same changes as CD28 with decreased expression as T cells differentiate (Koch et al., 2008; Hazenberg et al., 2001; Ferrando-Martinez et al., 2011).

As such, CD27-/CD28- T cells represent highly differentiated effecter T cells that accumulate in old age. They have limited proliferative capability but as they are apoptosis resistant, an accumulation is seen with age, mainly in CD8+ cells (Vallejo et al., 2000). However, the proliferate capability of these CD27-/CD28- cells seems to be better preserved in the CD4+ population, because these cells maintain a certain antigen-induced telomerase activity (Valenzuela and Effros, 2002).

Another change seen in differentiated T cells in old age is the acquisition, mainly in CD8+ cells but also in CD4+, of NK markers, such as CD56 (Abedin et al., 2005; Fagnoni et al., 1996; Moro-Garcia et al., 2013). The presence of the NK cell markers is associated with an age increased presence of cytotoxic molecules (Brown et al., 2012) and allows CD28- T cells to be activated independently of TCR and maintain their cytotoxic capability remains diminished (Brown et al., 2012; Tarazona et al., 2002). There is a decreased output of regulatory T cells (Tregs) in thymic involution. Treg-mediated suppression has been reported to decline after the age of 50, which might contribute to age-related phenomena such as increased inflammation and autoimmunity (Tsakanridis et al., 2003).

### Diseases and old age

The basic functions of immunity, i.e., defence, homeostasis and surveillance are known to wear out as advances. Several studies have been shown that there is decline in resistance to infections against a wide range of pathogens mostly due to a T cell dysfunction. T cells have shown to support better protection to polio virus, tuberculosis, listeria, influenza and trypanosomes. Age associated alternations in systemic immunity contribute
to the increased incidence and severity of infectious diseases in older people (Castle, 2000). Infectious diseases are disorders caused by organisms such as bacteria, viruses, fungi, or parasites. The mechanical barrier, the skin, is the first line of defence against invasion and shows signs of thinning of epidermis and decreased granular secretions resulting in more infections following in trauma and injuries in older people. Infection may occur early in life and persist for years/decades if not cleared from the organism. This is the case of cytomegalovirus (CMV). This is one of the most immune dominant antigens that stimulate immune responses of unprecedented magnitude. CMV is asymptomatic in most individuals and only in rare cases CMV disease develop (Cannon et al., 2010). Old age individuals experience accumulation of CMV specific CD8+ T-cells and reduction of the number and frequency of circulating naïve T-cells. The accumulation by clonal expression reduces the space for CD8+ T-cells carrying receptors that are specific for antigens other than CMV (Vezys et al., 2009). Some old age related diseases have been briefly described as follows:

**Tuberculosis**

The incidence of tuberculosis has been found to rise with age. The prevalence of tuberculosis in the elderly living community is twice the rate of younger population. It has been further observed that the failure rate of DOTs is significantly higher in the age group greater than 65 years than among patients in the 50 to 60 year age group. Skin tuberculin sensitivity test in elderly subjects show that the percentage of significant reactors to tuberculin declines with age (Creditor et al., 1998). This lowering in tuberculin reaction has been attributed to specific waning of CMI for tuberculin antigen, rather than to a generalized decline in cutaneous DTH in elderly patients (Gleckman and Hibert, 1982). It has been further observed that repeated boosting by tuberculin enhanced the percentage of tuberculin positivity in a progressive manner in aged people.

**Alzheimer's disease**

Alzheimer’s disease (AD) is an aging-related multifactorial disorder to which metabolic factors contribute at what has canonically been considered a centrally mediated process (Nuzzo et al., 2015). Although the exact underlying mechanisms are still unknown, yet histopathologically characterized by extracellular amyloids plaques formed by amyloid-β (Aβ) peptide and by intracellular neurofibrillary tangles. The inflammation resulting from deposits of highly aggregated Aβ plays a crucial role in the pathogenesis of AD (Akiyama et al., 2000). AD patients demonstrate changes in the distribution of lymphocyte subsets in the peripheral blood compared with controls coming from elderly donors, thereby the number of NK cells stay constant, whereas the number of T cells, especially the CD8+ population, and B cells decreases (Speciale et al., 2007). Neurological soft signs i.e. minor and sensory deficits are frequently found in Alzheimer’s disease due to deposition of intracellular protein names as neurofibrillary tangles and are comprised of hyperphosphorylated protein assembled in oligomeric structures called paired helical filaments (Morales et al., 2014). Inflammatory cytokines, which are important mediators of communication within the immune system, also act in the brain; they can activated microglial cells and astrocytes that in turn can produce cytokines, complement proteins and nitric oxide (Layé et al., 2015). In the brain, microglia express MHC class I and II molecules after activation. This can be caused by neurodegeneration or ischemia (McGeer and McGeer, 1995). By contrast, the activation of microglia in the brain of AD patients is caused by amyloid-β. As a result of the activation, the activated microglia luster at sites of amyloid-β deposition (Streit et al., 2004). It is known that microglia from elderly donors show changes in their cytoplasmic structure, which can lead to functional defects and thus to development of AD in the elderly, but still remains unknown how the activation of microglia is influenced by age and senescence (Streit et al., 2004).

**Cardiovascular Disease**

The aging process is accepted when metabolic and cardiovascular are present and this impacts on the susceptibility for other diseases (Novo et al., 2012). Cardiovascular heart disease is the most important cause of death in elderly individuals over the age of 65 years (Mathers and Loncar, 2006). Several risk factors that can contribute to heart disease include stress life style (e.g. lack of exercise, smoking and high consumption of alcohol), family history, obesity, hypertension, high cholesterol and diabetes. There are several types of cardiovascular diseases associated with aging. This is linked to higher prevalence of coronary disease, hypertension, diabetes, ventricular hypertrophy, fibrosis and aging/senescence of cardiac cells leading to events that may predict more severe cardiac failure (Lakatta and Levy, 2003; Chen and Frangogiannis, 2010).

**Cancer**

Immunosurveillance against cancer is daily fight of the immune system. It allows the killing of nascent tumour and the dissemination of cancer cells (Lustgarten, 2010). The incidence of cancer increases with advancing age (Myers et al., 2011). This is due to a cumulative number...
of events such as exposure to carcinogens, accumulation of mutations and diminishing of immune function. Among the alterations that diminish immune function, the generation of tumour specific T cell immunity against synergetic tumours decline with age (Flood et al., 1981). With advancing age there is a risk of getting cancer (Miller, 1980; Ershler, 1993). However, whether immune deficits in old age constitute to the increased incidence of cancer is debatable. Although majority of cancers occur in patients over the age of 65 years, there is yet no conclusive satisfactory explanation available to explain for the increased risk of cancers with advancing age.

Autoimmunity in Aging

Several types of diseases, among others autoimmune illness, could be coupled with the general process of aging (Urban et al., 2002). During cellular and molecular level alterations and thymic atrophy, immunosenescence is characterized by changes in T cell subsets resulting in a decline of T and B cell function. Thus there is a loss of ability to recognize “self” and “foreign” antigens. Therefore, the development of autoimmune response like production of auto antibodies (Prellog, 2006) is affected. Several researchers have reported an increased anti-nuclear (ANA), anti-mitochondrial (AMA), anti-smooth muscle (SMA), and anti-gastric parietal cells (PCA) antibodies in the sera of selected healthy elders(Nilsson et al., 2006; Potocka-Plazak et al., 1995).

CONCLUSIONS

The immune system changes with age. Both HI and CMI to foreign antigens are lowered with enhancement of “self” recognition. This phenomenon is associated with involvation of thymus gland creating an altered state of immune function. It is known that elderly people present increased susceptibility to infections (Gavazzi et al., 2004) and decreased responses to vaccination (Roukens et al., 2011) and poorer responses to known and new antigens. Additionally, aged individuals tend to present a chronic low-grade inflammatory state that has been implicated in the pathogenesis of many age-related diseases such as atherosclerosis, Alzheimer’s disease, cardiovascular disease, osteoporosis, cancer, and diabetes. Without any major health problems, some persons reach to advanced ages and are referred to as healthy aging. Therefore, there is an immediate need to apply all modern advanced techniques of immunology in gastrological research because in the modern world there is already a rise in the number of elderly people. Probably due to genetic and environmental factors the immune system dysfunction is somehow mitigated in this population which is yet to be described.

Conflict of Interest

The authors confirm that this article content has no conflicts of interest.

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