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IMMUNOSENESCENCE AND INFLAMM-AGEING

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Abstract

Researches on ageing phenomenon offer significant information regarding the consequences of stressors on immune system that affects longevity in the elderly. Immunosenescence has become the most common immunodeficiency state in humans, occurring in over 30% of community - dwelling elderly, and greater than 90% of elderly who are ill, taking medication, or residing in long-term care facilities. Immunosenescence may reflect tandem changes in neuroendocrine responses. There are several aging-related changes in cortisol, DHEA and catecholamines, which are considered to set up a "vicious cycle of endocrinosenescence and immuno-senescence". The low-level, chronic increase in innate, inflammatory response observed in older adults ultimately results in tissue damage and disease; the key inflammatory mediators in this process are CRP, nuclear factor (NF)-kB, IL-1-beta, IL-6, TNF-alpha, cyclooxygenase-2 (COX-2), and inducible nitric oxide (NO) synthase. Further, glucocorticoid inhibition of IL-6 production was observed to be lower in older compared to younger men following psychological stress. There are individual differences that protect aged people from stressors and strains, and it will be important to identify biological mechanisms of protection and those at risk who might benefit from early behavioral interventions.

Key words: aging, neuroendocrine, immunosenescence, endocrinosenescence, inflamm-ageing, pineal, stress.

Human life expectancy has almost doubled in developed countries during the past century and is continuing to increase at a rate of 2 years per decade (1, 2). Nevertheless, even though life expectancy has expanded, advanced age is accompanied by a rise in susceptibility towards infection and development of chronic illnesses that have a negative impact on an individual's quality of life. Older people (aged 65 years and over) in Romania represented almost 10% of total population in 1990, i.e. nearly 1 in 10 people was beyond the age-threshold between adults and elderly (3) (Fig. 1).

In 2008 it was estimated that 15% (1 in 7 persons) in Romania were more than 65 years old but in 2011, after the national census (4) – a total of 16.1% people were beyond the age of 65 years

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(total inhabitants: 20,121,641; 51.3% feminine gender; 54% urban) and 1.3% were older than 85 years. Nevertheless, one needs to take into account the process of emigration that also contributed to this high percentage of older people in Romania. Nearly two million of members of younger generations are considered as emigrants to various countries, mostly in Europe. This phenomenon produced somewhat an imbalance in the process of demographic ageing, especially in rural areas where older people became much more prevalent as compared to urban areas (4). Another important aspect is a high prevalence of rural population as compared to other European countries: almost 46% (5). One aspect that contributed to demographic ageing in Romania was an increased life expectancy from around 70 years in 2000 to 74.51 years in 2011 (Fig. 2), 78 years for women and 71 years for men (4) (Fig. 2).

Ageing is considered a continuous and slow process that affects the normal functioning and structure of various organs and systems, including the immune system, in both qualitative and quantitative terms. One of the most important components of immune defense is represented by inflammation. After taking contact with non-self antigens, cells of the inflammatory response (effector cells) release signaling molecules called pro-inflammatory cytokines that amplify the response by recruiting other macrophages and granulocytes to the site of infection. Therefore these cytokines can be considered as triggering signals. The inflammatory process continues as long as effector cells produce pro-inflammatory cytokines. To prevent inflammatory damage, another set of signaling molecules have the function of turning the process

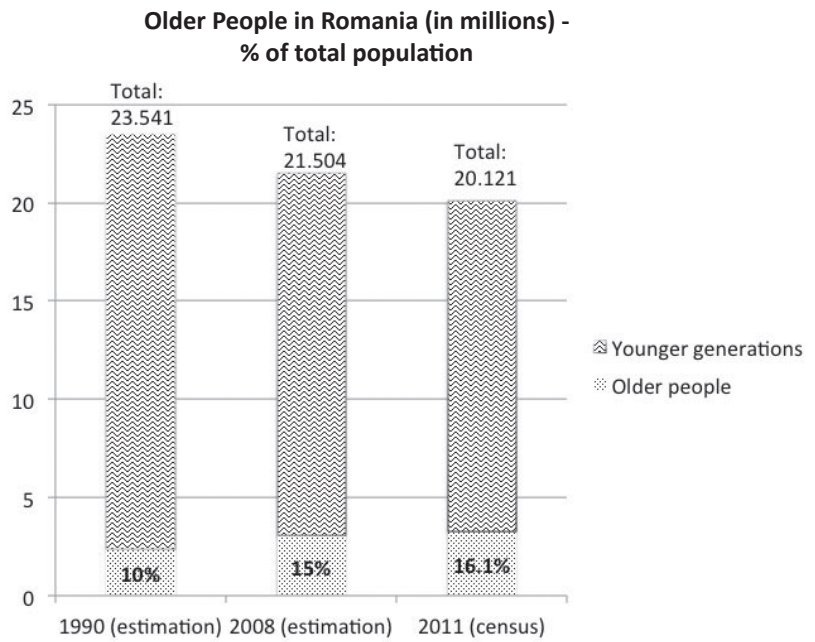

Figure 1. Older People in Romania (in millions) – prevalence in total population (3).

off. Therefore, these regulatory, anti-inflammatory cytokines play an essential role in maintaining organism homeostasis during the infection (6). Some important changes in the immunologic response occur with ageing (7-10). The number of naive T lymphocytes declines with age making the elderly less able to respond to novel antigens (8, 11). Senescent immune profiles are usually also characterized by an increase of inflammatory markers (12, 13), that might be produced by an impaired regulation (14).

During recent years, a growing body of studies has demonstrated that ageing down-regulates immune functions, a process known as immuno-senescence. Even adults considered to have undergone healthy ageing show a significant decline in immune competence, termed immunosenescence, which is responsible for the increased rate of infections with advancing age (15). Immunosenescence is represented by a decrease in both innate and adaptive immune response accompanied, on the one hand, by reduced pathogen recognition, chemotaxis, phagocytosis and, on the other hand, by diminished naive T-cell number, cytotoxicity, antibody quality and quantity (Fig. 3). Increasing age also leads to elevated basal levels of inflammation a process called "inflamm-ageing" (16) (Fig. 3). Inflamm-ageing is considered a state of increased low-grade chronic inflammatory status that means an increase in interleukin (6), tumor necrosis factor alpha and stress hormones (cortisol, epinephrine/ adrenaline, norepinephrine/noradrenaline). Inflamm-ageing is the end result of a process characterized by activation of macrophages and expansion of specific clones (megaclones) of T lymphocytes directed toward antigens of common viruses such as cytomegalovirus

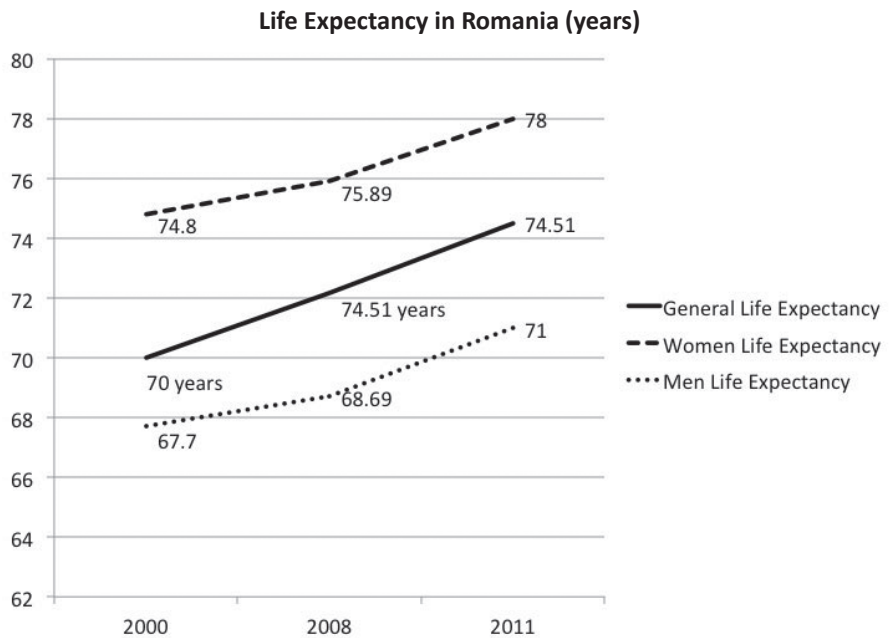

Figure 2. Evolution of Life Expectancy in Romania (4).

or Epstein-Barr virus (17) (Fig. 3). Consequently, immunosenescence and inflamm-ageing are associated with a heightened morbidity and mortality often seen in older people (18).

Some authors consider that ageing is accompanied by two major imbalances in healthy, normal immune function (Fig. 3): a chronic inflammatory state (inflamm-ageing) and a decline in adaptive immunity (19). Recent studies have also reported a reduced ability to mount a robust immune response to vaccination, combat new pathogens and maintain immunity to persistent infections such as Herpes zoster in older adults (20-22).

The clinical consequences of immunosenescence may include increased susceptibility to: infectious diseases, neoplasias, metabolic diseases, osteoporosis and autoimmune diseases (23, 24). This increased morbidity is not evenly distributed and seems to be influenced by other immune-modulating factors, including genetic background and chronic stress exposure (25). Indeed, psychological stress appears to be an important factor leading to earlier onset of many age-related diseases (17). Although factors that initiate psychological and physical stress differ, the ways in which they impact the immune system are similar and include activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic adrenal-medullary (SAM) axis, both of which influence the immune system. Therefore, a better understanding of how stress is likely to promote 'biological ageing' may lead to clinical interventions or policies with a broad public health impact. An important aspect connecting immunosenescence to increased risk of

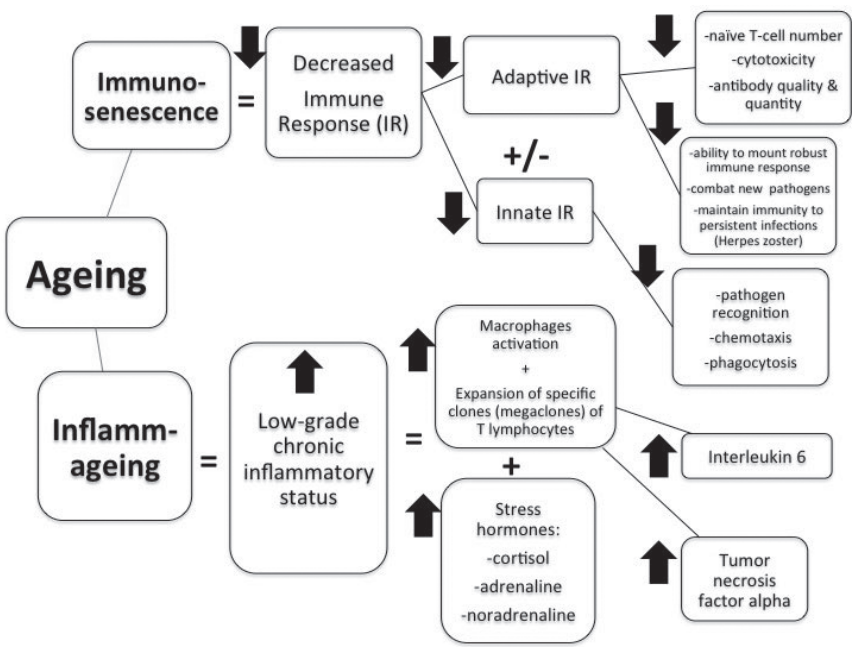

Figure 3. Ageing, Immunosenescence and Inflamm-ageing (16 -18).

neoplasia is the role of pineal gland in tumor growth inhibition (26). Melatonin, the major hormone of this gland, is involved in tumor inhibition (27, 28), but it is suppressed by light exposure at night and this is also accompanied by circadian disruption. Moreover, sleep is often impaired in older people and melatonin levels diminish with advanced age. In addition, neoplasias are more often seen in older people and all these phenomena might be connected. The role of pineal gland in inhibiting the growth of various tumors might be more complex than initially deemed. Besides melatonin, there is growing body of evidence that other pineal gland factors may have tumor growth inhibiting properties (26) and this might at least in part explain the higher prevalence of neoplasias in older people.

There is also evidence suggesting that ageing is associated with activation of the hypothalamic–pituitary–adrenal (HPA) axis (29), leading to increased cortisol levels in man. The HPA axis is a major stress-responsive system and higher cortisol levels are also found during chronic stress or major depression. Immunosenescence may be influenced by both psychological stress and stress hormones. Indeed, most cellular and molecular changes observed during immunosenescence are similarly found during chronic stress or chronic glucocorticoid exposure (30). Psychological stress may lead to premature ageing at various levels (29): molecular (increased oxidative stress, decreased telomerase activity and shorter telomere); cellular (increased regulatory T cells and decreased naive T cells and B cells, also reduced T-cell proliferation, natural killer cell activity and sensitivity to glucocorticoids); systemic (neuroendocrine - increased cortisol and decreased dehydroepiandrosterone, lymphoid organs with thymic involution and inflamm-ageing with increased pro-inflammatory cytokines, soluble cytokine receptors and acute phase proteins); populational with increased morbidity (infections, hypertension, cardiovascular disease, poor wound healing) and mortality.

A series of studies on ageing provide important information regarding the effects of lifetime stressors on the immune system that might control longe-vity in older people (19). During the previous century, immunosenescence has become the most common immunodeficiency state in humans, occurring in more than 30% of the community-dwelling elderly, and over than 90% of older people who are: ill, taking medication, residing in long-term care facilities (31). Age-related endocrine changes named endocrinosenescence have important effects on immunosenescence, in particular, via age-related declines in: growth hormone (GH), sex hormones and dehydroepiandrosterone (DHEA). Immunosenescence may reflect complex changes in neuroendocrine responses. Some authors described ageing-related changes in a series of hormones, including stress hormones (cortisol, catecholamines) and DHEA, that Straub and colleagues (32) hypothesize to set up a "vicious cycle of endocrinosenescence and immunosenescence". This vicious cycle of endocrinosenescence and

immunosenescence has the following aspect: ageing and stress both impact endocrine and immune function, affecting regulation of inflammatory mediators and adrenal stress hormones. Regarding the immune system, there will be an increase of pro-inflammatory cytokines (interleukin-6, tumor necrosis factor alpha and interleukin-1) and of lymphocytes T helper-2 cytokines (interleukin 4, interleukin 10) and IgE. Moreover, there will be a decrease in lymphocytes T helper-1 cytokines (interleukin-2, interleukin-12 and interferon gamma). Concerning the endocrine system, there will be an increase in cortisol and a decrease in dehydroepiandrosterone sulphate and in adrenal epinephrine and norepinephrine output and clearance. The last process may result in high circulating levels of epinephrine and norepinephrine. Both immune system and the endocrine system will influence each other and they will increase susceptibility to inflammatory disease. Stress-related dysregulation of these systems may combine with age-related dysregulation to render older adults particularly vulnerable to inflammatory disease.

More and more studies regarding various approaches to counteract the negative effects of stress on immune function are published, with interventions ranging from stress-reduction to exercise. In one paper (33), geriatric residents of independent-living facilities were randomly assigned to three groups according to specific types of intervention: relaxation therapy, social support and control groups. Only relaxation therapy was followed by decreased distress and an increase in T-cell proliferation when incubated with the mitogen phytohemagglutinin. Another approach consisted of a brief intervention involving expressive writing about previous stressful life events. It also generated positive changes in immune function, such as increased antibody responses to hepatitis B vaccine in medical students (34) and a reduction in global activity of the disease in patients with rheumatoid arthritis (35).

Several papers demonstrated that exercise has immune-enhancing effects, especially in older subjects. In a study regarding the response to influenza vaccine, previously sedentary older people were randomly allocated two groups: one group performed cardiovascular exercise while the other followed a flexibility and balance training. Only the subjects from cardiovascular exercise group showed a longer-lasting seroprotection 6 months after vaccination (36).

Besides improvement in antibody response to influenza vaccination, exercise can reduce inflammation in older people. Some authors (37) noticed that cardiovascular exercise unlike flexibility training for previously sedentary older adults resulted in significant reductions in proinflammatory serum C-reactive protein, interleukin-6, and interleukin-18, even after adjustment for body mass index, which is positively associated with inflammatory cytokines and C-reactive protein.

There are a series of protective and risk factors, as well as interventions associated with accelerated aging of the immune system. Protective factors

are represented by coping skills, social support network, positive affect and active behaviour. Interventions aimed at reducing ageing of the immune system are: stress management, dehydroepiandrosterone therapy, moderate exercise and acupuncture. Several risk factors are involved in premature ageing of the immune system such as: higher anxiety, inhibited personality, smaller social groups, low self-esteem, poor health-related lifestyle. They act through stress-related increase in the ratio between cortisol and dehydroepiandrosterone. Accelerated immunosenescence will be ultimately involved in increased morbidity, mortality and reduced life expectancy. Conversely, the maintenance of active behaviours, moderate exercise, large social support, adequate personality (positive mood), suitable coping skills and involvement in stress-management interventions may protect older people from deleterious effects of exposure to chronic stress. Delaying or reversing the effects of ageing on the immune system may therefore be extremely beneficial to the health and quality of life of older population (38, 39).

Human studies in psychoneuroimmunology underscore the multiple ways in which the bidirectional influence of the central nervous system and immune system impacts well-being. Further, human studies indicate that stress-induced changes in immune function – including shortened telomere length and increased inflammation – begin to accumulate in early childhood. There are individual differences that protect some people from the stressors and strains. It will be important to: better determine what those factors are and to identify: the biological mechanisms of protection those at risk who might benefit from early behavioral interventions.

Conflict of interest

The author declares that there is no conflict of interest.

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