

Review

Immunosenescence and infectious diseases

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ABSTRACT – Infectious diseases are major causes, with malignancies, of morbidity and mortality in the elderly. Increased susceptibility to infections may result from underlying dysfunction of an aged immune system; moreover, inappropriate immunologic functions associated with aging can determine an insufficient response to vaccines. Impairments of cellular, humoral and innate immunity in the elderly, contributing to increased incidence of infectious diseases, are discussed in this review. © 2001 Éditions scientifiques et médicales Elsevier SAS

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1. Immunosenescence

Aging is associated with a decline in a large number of physiological functions, as well as immune function. Deterioration of immune response is designated 'immunosenescence' and is found in both long- and short-living species as a function of their age relative to life expectancy rather than chronological time.

There is increasingly good evidence that immunosenescence contributes to morbidity and mortality in man because of the greater incidence of infection. In fact, many studies have suggested a correlation between immune function and age-related risk of morbidity and mortality [1]. Clinical observations indicate that elderly people are prone to severe, often lethal, infectious diseases induced by novel pathogens. Infections of respiratory and urinary tracts, endocarditis, septicemia and tuberculosis are commonly encountered in the elderly; moreover, atypical clinical presentations, slow response to treatment and high mortality are all marks of infection in elderly subjects [2]. Clinical evidence indicates that with advancing age, immune responses against recall antigens may still be conserved, but the ability to mount primary immune responses against novel antigens declines significantly [3]. The impaired ability to mount immune responses to new antigens may result in a high susceptibility to infectious diseases and may limit the efficacy of vaccination strategies in elderly people.

The study of the aging immune system in man has often led to differing and contradictory results because aging is a slow process and it is difficult to choose appropriate criteria for assessing it. A source of discrepancies is the selection of investigated donors who could be affected by

disease, influencing the immune system and thereby the results. To obtain insights into the effects of aging on the immune system, it is therefore of great importance that the true aging process be free from the influences of underlying disease and the use of medication. Thus, only healthy elderly subjects, selected by strict admission criteria, should be considered a reference population to study the intrinsic effects of aging [4].

The age-related immune findings we consider in this review refer essentially to healthy elderly subjects. Of course these alterations typical of immunosenescence could represent the physiopathologic condition which predisposes the elderly to a wide range of infections and other diseases. There is a strict association between immune function and individual longevity. A Swedish longitudinal study [5] showed that non-survival was associated with the clustered parameters of poor T-cell proliferative response, high CD8 cytotoxic/suppressor cell fraction, and low CD4 helper/DTH cells and CD19 B cells. No single parameter could be used to predict survival, but a cluster of the above parameters was an effective predictor of mortality. More recently, in a Dutch cross-sectional study, it was demonstrated that CD4 lymphopenia (< 400/ μ L) in the oldest individuals resulted in a twofold increased mortality risk over the first 2 years following diagnosis [6]. Other data illustrating the importance of the immune system in healthy aging come from studies on centenarians. By and large, unlike the 'average' younger elderly, healthy centenarians are found to have well-preserved immune functions, more similar to those of the 'young' immune system [7].

Words such as alteration, deterioration and decline do not account for the complexity of immunosenescence, since some immune parameters increase, others decrease and still others remain unchanged, so that the term 'continuos remodeling' would be more appropriate [7].

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Therefore, a better understanding of the causes of immunosenescence, particularly why a very small proportion of individuals seem to avoid it, may offer the possibility of therapeutic intervention. Amelioration of the effects of dysregulated immune responses in elderly people may result in an enhancement of their quality of life, and significant reductions in the cost of medical care in old age.

Aging of the immune system involves both humoral and cell-mediated immunity; ancestral innate immunity is also largely modified with age. The principal changes in cellular immunity due to aging are as follows: decrease in CD3, CD4 and CD8 absolute number; increase in activated peripheral T cells (HLA-DR⁺); decrease in naive T lymphocytes (CD45RA⁺); alterations in signal transduction through TCR; impaired PHA-induced lymphocyte proliferation; Th1 to Th2 cytokine production shift and increase in expression of several CAMs.

The changes in humoral immunity due to aging include: increase in the level of serum immunoglobulins (particularly IgA and IgG, except IgG4 subclass); decrease in the number of total B lymphocytes; decrease in organ-specific autoantibodies; increase in non-organ-specific autoantibodies and decrease in high-affinity protective antibody response.

The changes in innate immunity due to aging include: increase in NK cells; decrease in NK cell function; functional alterations in neutrophils; organ-specific defects in macrophages; decrease in macrophages required to optimal T-cell response and increase in production of proinflammatory cytokines by mononuclear cells.

2. Cellular Immunity

Even when the percentages of the main T-cell subsets remain unchanged in most aged donors, the absolute number of CD3, CD4 and CD8 T cells decreases with age, whereas activated peripheral T cells (HLADR⁺) are markedly augmented [8]. Moreover, T-cell function is markedly decreased in elderly compared to young individuals. The decline in T-cell function is considered a result of thymic involution [9, 10]. The effect of age-related involution on the kinetics of thymocyte differentiation could depend on an intrinsic defect within the thymocyte population or a deficiency in the ability of stromal cells to support differentiation or defects in lymphokine-driven thymocyte proliferation.

The immune responses to novel antigens rely on the availability of naive T cells. In order to mount primary responses to new antigens even in advanced age, i.e. a long time after the onset of thymic atrophy, naive T cells have to survive as long as long-lived resting cells from the time of their initial release from the thymus. Based on this assumption, the lifespan of these T cells in humans should reach several decades, especially when considering very old people such as centenarians. Alternatively, it should be hypothesized that in advanced age, naive T cells may still be provided by thymic remnants and/or by other organs which take over for the thymus or by peripheral thymic-independent pathways [3].

One of the most interesting observations in T cells of aging humans is a progressive shift from a predominance of naive to memory cells; an age-related imbalance of virgin and memory cells is found between CD4 and CD8 subsets [3, 11]. Naive and memory cells are defined by the mutually exclusive expression of the two isoforms of CD45 leukocyte antigen, respectively, CD45RA and CD45RO; these cells correspond to different stages of post-thymic T-cell development. Naive T cells preferentially migrate into lymphoid organs via high endothelial venules. Here they recognize the antigen and mount a primary immune response. By contrast, memory cells migrate into non-lymphoid organs, where they rapidly initiate a secondary immune response [12].

Naive T cells, identified as CD45RA⁺CD45RO⁻/CD62L⁺ T cells or characterized as CD95⁻ T cells require a costimulatory signal, such as CD28, to optimally proliferate after anti-CD3 stimulation [3].

Altered function and proliferative response of memory and naive T cells have also been observed during senescence [13]. An important implication of this observation is that specific immunization targeted at the naive cell population in aged individuals may not be effective, thus suggesting that strategies to vaccinate elderly individuals must take into account both the decrease in naive T-cell numbers and their decreased responsiveness [14]. This age-related hyporesponsiveness to new antigens reflects both a diminished residual population of available antigen-specific cells and a decreased functional capacity of the naive T-cell population.

A decrease in IL-2 production occurs with age, and this decrease could be interpreted as a result of changes in total number of T cells or a shift in one or more T-cell subsets. In fact, naive T cells produce higher levels of IL-2 than do memory T cells in response to mitogen stimulation, and it is possible that the decline in the number of naive T cells during aging is responsible, at least partially, for the age-related decline in IL-2 production [15]. The entire cytokine network undergoes profound and complex changes with age, and production and utilization of some cytokines decreases with age, whereas the production of other cytokines increases.

Cytokines, produced by two general subsets of helper cells known as Th1 and Th2, regulate the immune response. Th1 cells provide help for CD8-mediated cellular function and the IgG2a class of antibody, Th2 cells help B cells and the IgA, IgE and IgG1 classes of antibodies. Th1 cytokines include IL-2, IFN- γ , IL-12 and IL-15, Th2 cytokines are IL-4, IL-5, IL-6, IL-10 and IL-13 [15].

The main findings in the elderly are a Th1 to Th2 cytokine production shift; particularly, IFN- γ production is reduced and IL-4 production is increased, accompanying diminished influenza virus-specific CD8⁺ cytotoxic T lymphocyte responses, among elderly subjects compared to young individuals.

The reduced production of IFN- γ could be a consequence of the decrease in CD45RO⁺ T cells which produce this cytokine; these age-related changes could be more dramatic at the tissue level and contribute to the impaired delayed-type hypersensitivity (DTH). On the whole, the association between dysregulation of cytokines

and functional immune defects observed during aging is still unclear, but it could interfere with the ability of the host to respond to a specific infectious challenge.

During aging there is an impaired response of PHA-induced lymphocyte proliferation and its degree correlates with age; although this reduced proliferation may partly be a consequence of diminished IL-2 production, other alterations such as those in signal transduction through the T-cell receptor (TCR) complex may determine the age-related hyporesponsiveness of both memory and naive T cells [8].

These functional alterations could be partly explained by altered expression of cell surface molecules; in fact, several important receptor molecules are differentially modulated on specific subsets during senescence [16]. For example, CD3 is downregulated on both memory and naive cells. The membrane expression of certain molecules on the lymphocyte surface involved in the homing process, and of several cell adhesion molecules, changes with age and could be involved in the increased susceptibility in elderly people to infections, cancer and autoimmune diseases [16]. Cell adhesion molecules (CAMs) are surface receptors mediating cell–cell and cell–matrix interactions. Cell adhesion is fundamental in lymphocyte functions including maturation, circulation and homing, generation of inflammatory responses and interaction of killer cells with their targets. Many CAMs also have regulatory functions and transduction properties. The expression of adhesion molecules by lymphocyte subtypes varies and in some instances is associated with the activation state of the cell. The modification of the number of CAMs on the cell surface, in addition to alterations in their affinity and avidity, provides the molecular basis for the interaction between different cells. These findings may contribute to the remodeling of immune system in aging [16].

Leukocytes from elderly subjects exhibit peculiar changes in expression of CAMs, particularly on T lymphocytes [12]; their different expression on the surface of cells from elderly, compared to young individuals, may lead to significant immune dysfunctions, but it could also be interpreted as an effort of immune cells to cope with a decreased responsiveness [7, 17, 18].

A recent study by Fagnoni et al. [3] demonstrates a decrease in naive T lymphocytes within the CD8⁺ T-cell subset in old people, particularly in centenarians. This exhaustion of naive T cells within the CD8⁺ T cells could account for the reduced competence to face new intracellular pathogens which occurs during senescence and may define an 'immunological clock' which is possibly correlated to the life span of humans. Class I-restricted CD8⁺ T cells play a major role in infectious diseases caused by pathogens living inside cells, and they constitute an important effector arm for immune surveillance against tumors. A few studies have also found a shortage of naive CD8⁺ T cells in HIV-infected adults. Infectious diseases such as influenza and pneumonia, and cancer are major health problems in older people and represent leading causes of death in this population. Therefore, naive CD8⁺ T cells constitute an important reservoir, and their shortage could predict lack of protection against novel class I-restricted antigens. Based on the loss of naive

T cells within the CD8⁺ compartment, it can be predicted that very old subjects have low protection against infectious diseases, especially viruses, and malignant cells. A high susceptibility to viral infections and a current short life expectancy both characterize far-advanced aged people. Aging is associated with expansion of CD28⁻ effector T cells [19]. They may be generated from extrathymic lymphopoiesis, or alternatively, they may derive from loss of the CD28 molecule by thymus-derived T cells. [3]. Recent studies on T-cell regeneration in different clinical settings have shown that thymic-independent expansion of a mature T-cell population may represent the primary pathway by which T cells are regenerated. Reminiscent of what is seen after toxic assaults from chemotherapy, irradiation or infections such as HIV, it is possible to hypothesize that during aging, when the ability to replenish the naive pool via thymopoiesis is reduced, the immune system tries to compensate for the progressive loss of naive T cells by increasing thymic-independent pathways, such as the peripheral expansion of mature CD28⁻ T cells, especially within the CD8⁺ subset. Taken together, these age-dependent changes in the T-cell subpopulations indicate that advanced age, per se, is a condition characterized by lack of adaptive immune response to new intracellular pathogens. These changes also strongly support the notion that aging shares similarities with persistent and chronic stimulatory conditions of the immune system by infectious agents such as HIV.

The age-related thymic involution, with the consequent age-related decrease in output of new T cells, leaves the body devoid of virgin T cells, then likely more prone to a variety of infectious diseases, primarily bacterial infections (pneumonia and urinary tract, skin and soft-tissue infections) and some viral infections (reactivation of herpes zoster and influenza virus). Moreover, the age-related immune dysregulation creates difficulty in detecting both active (primary infections and reactivation) and inactive tuberculosis.

Naive T-cells are quiescent, but must maintain active metabolism. They need to protect themselves both against intrinsic factors resulting from their metabolism, as well as extrinsic factors such as background irradiation or chemical assault. These protective mechanisms seem to decrease in effectiveness with age and can result in cell death due to damage accumulation. Normal somatic cells are capable of a limited number of rounds of cell division before growth cessation occurs. The T-cell immune system is particularly sensitive to this so-called 'replicative senescence' because of the intrinsic nature of the immune response. Thus, resting naive cells must be stimulated to extensive proliferation in order to generate an adequate immune response; memory cells must thereafter be maintained in a state of slow proliferation, during which they also 'use up' their proliferative capacity; and, finally, the re-exposure to antigen results in another round of extensive clonal expansion of the memory cells [3].

This estimate assumes memory maintenance in the absence of antigen. Antigen rechallenge would then not be required to boost the memory cells, but to educate new naive cells which had differentiated in the meantime. Theoretically, vaccination boosting might actually further

reduce the life span of the memory cells, but would sensitize T-cells which had developed after the last exposure to antigen; its effectiveness would depend upon the availability of new naive T-cells. However, an ever-decreasing output of naive cells from the aging thymus would imply decreased efficacy of vaccination in the elderly. This 'memory burnout', though, depends on whether all memory cells are activated and then reformed from the 'secondary effector pool' or whether only a fraction of memory cells starts dividing, thereby leaving some memory cells as reserve. In the latter case there would be no problem. The observation that repeated influenza vaccinations with the same antigen do not reduce immune responses in the elderly may provide evidence that 'memory burnout' is not necessarily a clinically relevant problem. Conversely, re-exposure to the antigen does not seem to be necessary to maintain immunologic memory [3].

3. Humoral immunity

Alterations of the B-cell compartment observed during aging cause humoral abnormalities and immunological manifestations such as hypergammaglobulinemia, autoantibody production, autoimmune manifestations and lymphoproliferative diseases [17]. The marked susceptibility of elderly subjects to infectious diseases (pneumonia, influenza, gastroenteritis, bronchitis) and poor response to vaccines [8] results from this altered antibody response. Recent studies show how reduced humoral responsiveness and altered antibody-mediated defense mechanisms observed in aging are due not only to decreased helper T-cell function but also to an intrinsic primary B-cell deficit [20].

In the elderly, increased levels of serum immunoglobulins are observed [17]; particularly, IgG and IgA serum levels show a significant increase; in healthy old people and centenarians, these two antibodies may confer greater protection against viral and bacterial infections. Interestingly, very few IgG subclass defects were found in elderly subjects, except for IgG4 deficiency [20]. In fact, among IgG subclasses, IgG1, IgG2 and IgG3 are most significantly augmented, whereas IgM is not increased [20]. IgG1 and IgG3 are mainly involved in the humoral responses to viral and bacterial antigens. IgG2 and IgM are involved in responses to polysaccharides (mainly outer wall antigens of capsulated bacteria), and IgG4 and IgE are mostly related to parasite antigens, also being the 'memory' isotype in conditions of chronic high-dose exposure.

In elderly subjects a decreased number of total B lymphocytes and B cells coexpressing the CD5 molecule was found despite the observed hypergammaglobulinemia [21]. These findings also apply to centenarians, who are the best example of successful aging, since they have escaped major age-related diseases and have reached the extreme limit of human life.

The CD19⁺CD5⁺ B-cell subset can be at the origin of B lymphocytic leukemia [17] and can be involved in the production of polyreactive autoantibodies and autoimmunity. Polyreactive autoantibody production opens the com-

plex problem of autoimmunity in aging. Franceschi et al. have shown evidence of the absence of organ-specific autoantibodies (antithyroperoxidase and antithyroglobulin) not only in the plasma of healthy centenarians who displayed complex changes in thyroid function, but also in healthy old subjects. Non-organ-specific autoantibodies (anti-dsDNA, antihistones, rheumatoid factor, anticardiolipin) seem to follow a different trend by increasing in healthy aged donors and centenarians. The age-related changes in the level of autoantibodies and B cells can be explained by a number of different possibilities, including: a) an increased number of B and plasma cells in organs other than peripheral blood; b) an increased life span of B and plasma cells in germinal centers; c) an increased production of Ig per cell [17]. Moreover, a diminished ability to generate high-affinity protective antibody responses to immunization against infectious agents or experimental antigens has been observed. Evidence has been accumulated suggesting that different immunoglobulin V genes may encode these antibodies and that the mechanism of somatic hypermutation in the V genes is inefficient. Somatic hypermutation in B cells is a principal event in the process of affinity maturation of the antibody response. Signaling dysequilibrium from aged T helper cells could provide less efficient help in quantitative terms while supporting the growth of B cells that express low-affinity receptors for the antigen [22].

Several alterations of the B-cell compartment can be associated with the profound changes in the production of a variety of cytokines, typical of aged people and centenarians, and several studies showed how the ability of T cells to promote B-cell activation and antibody production decreases with advancing age [17].

One of the aspects involved in altered interaction between T and B cells seems to be the contact-mediated help. Experimental evidence shows how T cells from aged mice need surface structures, particularly CD40L, for effective delivery of contact-mediated signals to resting B cells. During aging the decline in humoral immunity and B-cell activation can be related to the decline in CD40L expression. Resting T cells do not express CD40L until activated [23], and it is possible that signal transduction defects in T cells from old donors may interfere with the steps leading to CD40L expression.

The second phase of T-cell help includes lymphokines like IL-2, IL-4, IL-5 and others, produced by activated T cells. These promote various stages in B-cell activation, proliferation and differentiation into antibody-secreting plasma cells. The decrease in IL-2 production with aging may contribute to the diminution of T-cell help for antibody production and, indeed, IL-2 can in some cases correct the age-related loss in antibody production *in vitro* [8, 20].

4. Innate immunity

Phagocytic function is the primary mechanism through which the immune system eliminates most extracellular pathogenic microorganisms, and macrophages with granulocytes play a critical role in primary resistance to infec-

tious diseases. The function of macrophages and granulocytes in the elderly is impaired; bacterial and viral infections are a more common cause of illness and death among aged subjects, and once infection is established, the elderly also have a diminished capacity to prevent its spread.

As regards polymorphonuclear neutrophils, a body of evidence has accumulated demonstrating a general decrease in functional activities of these cells: normal or impaired phagocytosis, chemotaxis, degranulation and a relatively preserved or slightly diminished intracellular killing activity in polymorphonuclear neutrophils from elderly individuals have been documented [15].

Particularly, Seres and colleagues have found that granulocyte-macrophage colony stimulating factor was unable to prime granulocytes from elderly compared to younger subjects for the activation of several parameters, such as superoxide production, intracellular calcium flux, antibody-dependent cellular cytotoxicity and intracellular killing mechanism, processes critical at the earliest phases of infections, influencing susceptibility to infection [24].

Organ-specific defects in mononuclear phagocyte (MP) function have been described in the elderly; in aged mice a lower clonal growth of alveolar macrophages has been demonstrated, compared to young mice. This could correlate with increased incidence of pneumonia, as well as decreased response to pneumococcal vaccine, which has been attributed to macrophage defects [25]. The absolute number of MPs is not diminished in the elderly, but more macrophages are required to elicit optimal T-cell responses to mitogen; therefore, the capability of mononuclear cells from healthy aged subjects, as well as from centenarians, to produce proinflammatory cytokines such as IL-1, IL-6, IL-8 and tumor necrosis factor α (TNF- α) increases with age [26].

The plasma level of IL-6 is very low in young subjects, it starts to increase in healthy people at about 50–60 years of age and continues to increase until the extreme limit of human life. This increase occurs both in people who enjoyed successful aging and those who suffered pathological aging [27].

High levels of IL-6 have been found in a high percentage of centenarians in good health; however, an increase in IL-6 has been referred to as the most powerful predictor of morbidity and mortality in the elderly. According to Franceschi et al. [27], we suggest that this paradoxical situation could be explained assuming that increase in IL-6 with age is the consequence of the successful adaptation to several stress factors, including infections, which occur throughout life. These authors call the global reduction of the capability to cope with a variety of stress factors and concomitant progressive increase in proinflammatory status characteristic of the aging process 'inflamm-aging'.

With regard to IL-8, which recruits MPs, its spontaneous production is decreased in the elderly, but it has been seen that the same men produce more IL-8 when the cells are stimulated with bacterial lipopolysaccharide; recruitment of massive numbers of mononuclear cells in the lungs, for example, may result in an increased pulmonary inflammatory response, which usually increases morbidity and mortality among elderly patients [25].

With regard to natural killer (NK) cell activity, a detailed cytofluorimetric analysis has demonstrated an age-related increase in the proportion of NK cells and CD56⁺ and/or CD57⁺ T cells (possibly of extrathymic origin) [7, 8]. NK expansion can be explained as a compensatory mechanism to overcome their decreased function; however, Krishnaraj et al. report, in agreement with several laboratories, that NK cell cytotoxic capacity of peripheral blood is highly preserved in the elderly [28]. Cells from centenarians can migrate perfectly in response to chemotactic stimuli and can kill target cells as well as can cells from young subjects, showing that innate immunity is not heavily deteriorated with age [15]. This is probably one of the reasons why healthy aged subjects such as centenarians are apparently fully capable of coping with infectious agents and show no increased susceptibility to infectious diseases, while elderly individuals who have an increased frequency of infections (influenza, tuberculosis, etc) are those in whom pathological changes in the immune system have occurred [15]. Recent data suggest that a persistently low NK activity is a predictor of morbidity; conversely, it can be speculated that well-preserved NK activity can help in becoming centenarians [7, 17].

Recognition of defects in constitutive immunity in the elderly may provide important opportunities for prophylactic intervention in these subjects. In fact, some compensation for defective immune responses during aging may be provided by vaccination. Many studies are being carried out to improve the preventive efficiency of vaccines in the elderly. However, the impairment of the immune system may limit the efficacy of vaccination strategies in the elderly. The vaccination problem should be addressed at the level of the antigen-presenting cell, because antigen-processing is defective during aging and it could be difficult to obtain an optimal response to vaccines in these subjects [25].

Therapy specifically targeted at defective phagocytic cell function, including the use of adjuvants with immunizations and nutritional supplementation, offers the opportunity to further enhance the ability of these hosts to resist infectious challenges. The importance of nutritional status in the integrity of the immune response is generally well recognized and should be taken into consideration in the case of elderly subjects [29]. Several micronutrients, including zinc, selenium and vitamin E, play an important role in phagocytic cell function; in particular, a zinc deficit has been associated with an increased risk of bacterial infections (the same deficiencies have been found in HIV-infected individuals) [25].

Many trials based on the experimental supplementation of diet in elderly subjects with one or more nutrients and vitamins have demonstrated an improvement in many immunological parameters: either in cellular immunity, such as the increase in DTH, increase in the number of helper T cells, T-cell proliferation [20, 29, 30], or in humoral immunity [29, 31]. Thus, achievement of optimal nutritional status in elderly subjects, often susceptible to malnutrition, could be a useful tool to improve immune response to vaccination.

Another type of manipulation, which seems very successful in improving the immune function of aged rodents,

is hormone replacement or supplementation [20]. Melatonin supplementation has been utilized by the general public in an uncontrolled fashion with dubious and unproven benefits. The antioxidant effects of some of these products (vitamins and melatonin) which help to restore cell redox balance might be responsible for, or contribute to, the benefits observed in some experimental models and trials [20, 32].

Furthermore, impaired T-cell responses could be enhanced by means of cytokine immunotherapy; in fact many functional deficits of lymphocytes from elderly people are mediated by a cytokine imbalance. For example, IL-12, produced by macrophages and other antigen-presenting cells, is a pivotal cytokine with multiple immunoregulatory properties that stimulates Th1 cytokines; IL-12 cytokine immunotherapy, generally or in association with influenza vaccination, could enhance cytotoxic T lymphocyte responses and reduce influenza morbidity and mortality among high-risk elderly persons [15, 28].

Also, the administration of IL-2, which seems to be defective in the elderly, has been found to have some benefits, at least in 'in vitro' experiments and in animal models [20]. Regarding the use of adjuvants with immunizations, evidence has suggested that influenza antigens delivered with immunostimulatory complexes in aged mice results in a more protective response and a faster recovery from illness has been found in aged mice receiving the adjuvant-associated vaccine than in mice receiving the current influenza vaccine [33].

5. Immunosenescence and infectious diseases

Diagnosis of infections in the old individual is often difficult and antimicrobial strategies may have to be altered in this patient population. A problem of infections in the elderly is that they frequently present with non-specific signs and symptoms, and clues of focal infection are often absent or obscured by underlying chronic conditions. Antibiotic therapy in the elderly needs to be early, empirical and broad-spectrum through the parenteral route, with early changeover to oral therapy [2]; as to the choice of antibiotic drugs, aminopenicillins and cephalosporins are safer for the elderly than aminoglycosides.

Furthermore, changes in immune response may be clinically relevant to the reactivity of the elderly to vaccination against microorganisms; in fact, response to vaccine requires intact cell-mediated immunity to drive the humoral response. In particular, an impaired response to influenza virus infection, declines in antibody response to influenza vaccination, and frequent onset of illness in elderly subjects who underwent this kind of prophylaxis, are common observations [8]. Both primary and secondary antibody responses to vaccination have been impaired, the degree of impairment being greater when T-cell involvement is required to drive the antibody response (usually related to the complexity of the antigen).

Influenza is a major health problem among elderly people in industrialized countries; an estimated 90% of

the 10 000–40 000 excess deaths attributed to influenza annually in the United States occurs in subjects aged > 65 years [34].

Chronic illnesses such as emphysema, diabetes or chronic renal insufficiency also increase the risk of this infection, especially increasing the basal incidence rate of influenza virus pneumonia, and impair the response to vaccine.

Influenza vaccination has been shown to be effective in 33% of vaccinated elderly persons for preventing clinical infection and in 74% for preventing mortality [29]. Not only is the response to influenza vaccination inferior in the elderly, but also the level of protection from infection is lower than that in younger adults, which is probably related to the quality of the antibody produced in neutralizing viral pathogens. However it needs to be emphasized that vaccination of people aged > 65 years has been effective in reducing adverse events, despite the low efficacy in prevention of infections [34].

Fulop et al. [29] demonstrated a close link between nutritional status and response to influenza vaccination. In their study, nutritional parameters such as hemoglobin, hematocrit, total protein, iron and vitamin E levels, as well as DHEA were significantly lower in the nonresponsive group than in the responsive group. These results can help other nutritional intervention studies for improving the immune response by achieving an optimal nutritional status, mainly in the frail elderly population, which could have a great public health impact.

In any case, there is good accumulating empirical evidence that immunosenescence compromises protection against infectious disease in elderly people. This implies that an age-associated decreasing immunity results in increased incidence of those diseases that the immune system is designed to protect against, i.e. infectious diseases. This unsurprising conclusion suggests that preventing these infections using interventions designed to prevent or reverse immunosenescence could extend the period of life enjoyed in good health.

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