ISSN: 0976-3031

Available Online at http://www.recentscientific.com

CODEN: IJRSFP (USA)

International Journal of Recent Scientific Research
Vol. 9, Issue, 1(H), pp. 23416-23419, January, 2018

International Journal of Recent Scientific Research

DOI: 10.24327/IJRSR

Research Article

IMMUNOLOGY OF INFECTIONS AT THE PRESENT STAGE. IMMUNOLOGY OF CLIMAX AND AGING

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DOI: http://dx.doi.org/10.24327/ijrsr.2018.0901.1464

ARTICLE INFO

Article History:

Received 17th October, 2017
Received in revised form 21st November, 2017
Accepted 05th December, 2017
Published online 28th January, 2018

Key Words:

Older people, Immune Reactivity, Immune Aging.

ABSTRACT

The article considers the changes of immune response in pre- and menopausal periods and in old age, specific features of morbidity and its complications in elderly people, the state of key immune status factors in long-livers, the prospective methods of targeted correction of immune aging and treatment of elderly patients.

INTRODUCTION

Aging is a result of interaction between various endogenous and exogenous damaging agents with cell genetic material leading to a gradual accumulation of occasional mutations in a genome of somatic cells. There is a variety of theories of aging: somatic mutations, error catastrophes, DNA damage, protein damage, cross linking damage.

The Free Radical Theory of Aging

The theory suggests that various oxidation processes in a human body lead to an accumulation of oxygen active forms (a human being produces up to 1 ton of radicals during 70 years) causing multiple damaging effects to macromolecules and structures (nucleic acids, proteins, membranes, collagen, etc.).As a result, no more than four out of every million of superoxide radicals formed escape from the enzymatic protection, which, however, leads to the accumulation of aging-causing damaging factors, and the development of various pathological processes.

The Theory of Molecule Aging

Most molecules in aqueous solutions change over time, mainly as a result of interaction with other molecules and atoms (thermal motion, chemical reactions, α-radiation) and under the influence of electromagnetic radiation (ultraviolet radiation, γ-radiation). Molecules can decay into atoms, transform into other molecules, and undergo structural changes. The latter implies that functionally the molecule remains the same. However, the performance of the function may change. Deterioration of the molecule functioning over time under the influence of damaging factors can be considered as aging at the molecular level.

The Theory of Aging of Histocompatibility Antigens

These antigens are expressed on all nucleated cells of a body. The modification of these proteins induces rejection reactions - the greater, the more variations of signal molecules are pronounced.

The Theory of Immunosenescence

It is commonly known that thymus is the central organ of immunogenesis, however, it undergoes involution with age, which is accompanied by a progressive failure of the immune system (Anisimov, 2008).

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The Climax and Premenopausal Syndrome Immunology

A significant number of studies have appeared over the past 10 years, the results of which indicate menopause-specific immune disorders. Thus, it is shown that the development of the climacteric syndrome and its severity are largely determined by the hyperactivity of autoimmune reactions in relation to the ovarian components. The following RPHA values for antibodies against ovaries are suggested as criteria for the severity of this syndrome: mild - from 1:8 to 1:32; moderate - from 1:32 to 1:128; severe climacteric syndrome (CS) - above 1:128. The average $\log_2$ of the titer for CS was 70±8 at 7.18 in control.

In addition, the effect or function of the immune system declines and its regulatory component increases during climax and premenopausal period, at the age of 35-50 years. The absorbing ability is inhibited, while the metabolic capacity of phagocytes is activated, and an imbalance in the main classes of immune globulins develops, which indicates a decrease of the immune system capability.

The menopausal syndrome-related autoaggression is maintained by depression of T-cytotoxic suppressors with moderate activation of B-cells due to IgG hyper production. The CS complicated by obesity is accompanied by a decrease in the activity of phagocytes.

It should be emphasized that the immune status of those who suffer from menopausal syndrome is different in a certain way from changes in the immune system of older persons (over 70 years old). The first signs of age-related immunity dysfunctions are sometimes found in people of both sexes at the age of 50: hyperproduction of IgG and IgA antibodies with a decrease of common IgA and autoantibodies, a decrease in T-lymphocyte function, an increase in $CD8^+$-T-cells (suppressors, killers). Thus, the "censor" function of the immunity generally declines, which causes an increased frequency of oncological, autoimmune and infectious diseases of older people (Zemskov *et al*., 2016).

These data were the basis for successful use of thymalin, or tactivin, splenin in combination with vitamins E and C, glutamic acid for the correction of immunopathological changes and the symptoms of the climacteric syndrome [along with hormone replacement therapy] (Zemskov *et al*., 2007).

The Immunology of Old Age

There are external and internal factors of influence on the age-specific physiology of the immune response. Internal factors include heredity, neuroendocrine relationships, reactions to stresses, etc. External factors are various types of ionizing and radionuclide effects, ecological environment, unhealthy lifestyle, eating habits, etc.

The undoubted role of the connection between the aging processes and the state of the immune system is shown: 1. Progressive atrophy of the thymus, a significant decrease in the production of thymic hormones (polypeptides) and of the entire lymphoid system (spleen, lymph nodes) with the increase of years was detected. 2. With age, the number of "mature" T-lymphocytes in the thymus and peripheral blood is decreasing, while the number of immature and activated lymphocytes (a sign of inflammatory process) is increasing with a decline in the diversity of the antigenic repertoire of lymphocytes, and a decrease in the antitumor resistance of a human body. 3. The similarity of "age-related changes" and processes observed during early thymectomy and immunodeficiency states was revealed. 4. It is found that the ability of lymphocytes to be activated by the body's own cells is sharply reduced in elderly people, as well as in the experiment (old animals), that is, the controlling, "supervisory" function of lymphocytes in relation to the condition of their own organs and systems is significantly inhibited, as shown in the model of the syngeneic mixed culture of lymphocytes (Zemskov *et al*., 2015).

The rate of aging of a body as a whole largely depends on the state of the immunity central organ - thymus. Thymus reaches its maximum development by the 1st year of life. The average annual rate of thymic involution is 1 to 3%, which ensures reserve capacity of the organ up to a very old age (100 years and more). In newborns, $2 \cdot 10^9$ cells are constantly produced, 10^9 of which leave the organ. In adult people, these indices are 0.7 to 1.0%. The glandular gland reaches a mass of 30-40 g by the age of 10-15 years, then it gradually shrinks and weighs 10-13 g at 70-90 years. Adipose tissue replaces the functioning components of the thymus over time and only small areas perform a protective function at a great age. All parts of the immune system are progressively inhibited with age.

The Total Lymphocytes Count in Peripheral Blood

It sharply falls from 5 bln /l at an early age to 2 bln/ on l by 20 years. These quantitative parameters are then retained for the next 30 years of life. The number of lymphoid cells starts decreasing since the end of the fourth decade and goes down to 1.5 bln/l at the age of over 80 years. Notably, the maximum immune response is recorded during the pubertal period, while it is only 1-2% of the young people's quantity at an old age.

T-Component of Immune System

This link is particularly affected, which is associated with a decrease in the number of stem cells and a certain defectiveness of their functioning, which manifests itself in a decrease in the ability to migrate from the bone marrow to the central organs of the immune system, a greater sensitivity to ionizing radiation, etc. At the same time, the entry of old cells into the mitotic cycle is inhibited. The ratio of regulatory subpopulations of lymphocytes changes. The number of CD8+ lymphocytes decreases (according to other data, it is slightly increased) and remains normal or the content of CD4+ cells increases. All these disorders occur against a background of general lymphopenia.

Natural Killers

It is significant that a decrease in T-cell immunity with human aging is accompanied by the accumulation of this type of cells, which are the first line of defense in the system of natural immunity.

B-Lymphocytes

The population of these cells is rearranged with age. It is accompanied by a decrease in their circulating pool, a change in the antibody spectrum, its specificity, isotype, affinity and idiotype with a reduction of IgG with protective properties against pathogenic agents and concentration of "normal" antibodies. The primary immune response is most affected.

Vaccination produces low-grade antibodies of IgM class and only a secondary immune reaction at an old age is more secure.

Factors of Nonspecific Anti-Infective Resistance

These factors are inhibited to a lesser extent. The functional activity of macrophages, segmented neutrophils and bactericidal activity of neutrophilic granulocytes, although their total number does not change, decline. Oxygen metabolism in phagocytic cells of old people decreases by 45-70%, together with killer antibacterial protection. The activity of lysozyme, the total bactericidal activity of blood serum, and the formation of interferon fall down, while the inflammatory reaction becomes less pronounced. The content of complement increases in men in the sixth decade of life, in women - 10 years later, and then it decreases. The high sensitivity of elderly and very old patients to bacteria and fungi is due to population changes in these cells and a decrease in the proliferative response to stimuli. With age, the phagocytic index is more inhibited than the overall phagocytic activity. It extremely affects the intensity of intracellular killing of bacteria by active forms of oxygen.

Allergy

A study of a delayed-type hypersensitivity reaction of the elderly indicates a decreased reactivity to the antigens with which they contacted in youth. To this we must add suppression of type III allergic reactions (immunocomplex) and inhibition of IgE synthesis (type I allergy). At the same time, a decrease in the barrier function of the skin and mucous membranes facilitates easier sensitization of the body with chemicals, pathogens, their toxins, etc. All this increases the risk of bronchial asthma at an old age.

Immune Aging

Age-related changes in the immune system cause an increase in sensitivity to opportunistic viral and bacterial infections. They are based on an imbalance of memory T-cells with naive T-lymphocytes, a decrease in the proliferative response of T-cells, lack of a full-fledged response of B-lymphocytes, phagocytosis and natural killers, an increase in the synthesis of pro-inflammatory cytokines (interleukin-6, tumor necrosis α-factor). Specified mechanisms determine the clinical manifestations of age-related immunodeficiency in the elderly and old age - chronic inflammation (Semenkov *et al.,* 2006; Pokrovsky *et al.,* 2013).

The frequency of induction of autoimmune reactions quite expectedly increases in the elderly. This phenomenon is based on the intensification of somatic mutations and weakening of suppressor mechanisms, as a result of which immunocompetent cells become autoaggressive. Sometimes these conditions are associated with previous pathological processes, but they are more often induced in completely healthy individuals. Old people have antibodies against DNA, thyroglobulin, internal factor of the gastric mucosa, cell nuclei, mitochondria, myofibrils, cell membranes, lymphocytes, erythrocytes, pancreatic tissue, adrenals, liver, heart and brain. In women, the level of autoantibodies is higher than that in men, but their activity peak falls 10 years later (Semenkov *et al.,* 2006). Thus, the reticuloendothelial cells of the thymus gland are a control and clock mechanism regulating the duration of life. Long-livers are the immune elite, in whom the thymus involution is slowed down. A powerful factor in the immune system regulation is sex steroids. It is known that with the increase of age the gonadal function progressively decreases, which affects testosterone and estrogens production rate. It is most noticeable in men aged 70, and in women in postmenopause. However, in postmenopausal women, the ovarian continues the secretion of testosterone at a rate close to that of young women, with the exception of and other androgens, and in men over 40 years old the secretion of androstenedione adrenal androgens, especially androstenedione and progesterone, decreases. The circadian rhythms of luteinizing and follicle-stimulating hormones in the blood of elderly men are not determined, and in aged women the episodicity of hormone secretion during the day is not only unchanged but is also increased (I.I. Dedov, V.I. Dedov, 1992).

Morbidity in Old Age

Due to the fact that there is an almost twofold increase in the proportion of the elderly population in developed countries, the problem of treating these population groups seems to be quite urgent, as frequent examination and comprehensive treatment in its turn contributes to the increase in the incidence of patients, the risk of toxic effects of drugs due to deterioration of the corresponding systems, malignant neoplasms, immune disorders, etc. At the same time, on the one hand, there is a certain decrease in the frequency and severity of existing allergic disorders, and, on the other hand, due to age-related damage to mechanical barriers, there is induction of "new" pathological processes.

Age-related immunodeficiency is characterized by peculiarity of formation of clinical syndromes, more often infectious and autoimmune, less often allergic and immunoproliferative. Thus, in the elderly and old age, chronic recurrent bacterial, viral, fungal infections of the skin and mucous membranes develop (pyoderma, furunculosis, abscesses, herpes, candidiasis, conjunctivitis, stomatitis), chronic bronchitis, pneumonia, urogenital lesions (chronic vulvitis, pyelonephritis), gastroenteropathy with prolonged diarrhea, dysbiosis, prolonged subfebrile condition and fever of unclear etiology, generalized infections. Clinical manifestations of autoimmune syndrome appear in patients with rheumatoid arthritis, rheumatoid-like symptom complex, in patients with autoimmune cytopenia (thrombocytopenia, neutropenia, anemia), scleroderma, dermatomyositis, systemic lupus erythematosus, autoimmune thyroiditis, etc. (Zemskov*et al*., 2013).

In general, the structure of morbidity and mortality in persons over 60 years old is practically the same. The leading positions take cardiovascular, oncological, infectious and other diseases. They flow hard, rapidly, often become systemic and are hardly treatable. The problem of old age is degenerative diseases, especially neurodegenerative ones. Low-effective response of the body to vaccination and high sensitivity to pathogenic microorganisms at this age cause an increase in the frequency of infectious pathology with an unfavorable outcome. At this age, atherosclerosis becomes the main cardiovascular pathology, which contributes to the development of myocardial infarction, ischemic strokes, etc.

Specific Features of Immune Reactivity in Long-livers

Longevity is characterized by specific conditions manifested by

a high level of IL-6 and IL-18 pro-inflammatory cytokine which is involved in the body's defense reactions and the development of atherosclerosis, and IL-15 which is involved in the proliferation of memory T-cells. An increased level of coagulation factors in plasma (fibrinogen, von Willebrand factor), a decrease in proinflammatory and proatherosclerotic properties of platelets and an increased resistance to the inhibitory effect of homocysteine on the production of nitric oxide is noticed. A low level of lipid peroxidation in cell membranes as well as their high fluidity and the normal content of sialic acids is described. At the same time, a low serum concentration of Hsp70 heat shock protein, an increase in plasma of TGFP1 tumor necrosis factor (pleiotropic cytokine with strong suppressor activity against many inflammatory and immune responses) was registered. The researchers also noted an increased level of plasma cortisol (one of the most powerful anti-inflammatory substances produced in response to the effects of many stressors), a more frequent occurrence of B (III) blood group and a decrease in body mass index and fat content. The development of tolerance to carbohydrates, changes in the level of leptin, triglycerides, free fatty acids and low density lipids, an increase in IGF-1/IGFBP-3 ratio in blood plasma and the level of products of lipid peroxidation in low-density lipoproteins against the background of a decrease in resistance to oxidation (Anisimov, 2008) was reported.

Prospective Methods of Combating Immune Aging

Hormonal Compensatory Correction

Includes the use of sex steroids, melatonin, epithalamin, growth hormone, medicinal analogues of thymic factors (thymopoietin, thymosin) and preparations of tactivin, thymalin, thymogen, etc.

Cytokine Correction

Cytokine correction is carried out using preparations of interleukin-2 (roncoleukinum), α- and γ- leukocyte interferons, complex of cytokines (IL-1, IL-4, α-TNF), superlymph, colony-stimulating factors, myelopeptides.

Gene Cytokine Therapy

Has significant activity and includes transfection of the cytokine or its receptor gene by means of viral vectors.

Monoclonal Immunotherapy

It is based on suppression of proinflammatory and suppressor cytokine formation with the help of monoclonal antibodies.

Compensatory Nucleic Acid Therapy

Due to the fact that in the blood serum of the elderly there is a shortage of low molecular nucleic acids pool, it is recommended that sodium nucleate or appropriate diets are prescribed. Since the deficit of naive lymphocytes is formed in elderly people, the problem of vaccination effectiveness requires a solution. Indeed, in Austria, 40% of the elderly population did not have immunity to tetanus, though 50% of them had been vaccinated in the last 10 years, 25% - 5 years; they had a reduced response to primary and repeated vaccination, there were special features in immunizing with new antigens that they had not met before - new strains of influenza viruses, yellow fever, etc. (Semenkov *et al*., 2006). Considering fast and frequent formation of secondary purulent inflammatory diseases caused by influenza and other infections in elderly and senile age, the appointment of passive immunotherapy with specific or donor immune human globulins containing up to 180-200 complete and incomplete antibodies is recommended (Zemskov *et al*., 1977).

There are specific features of immunotherapy in gerontological practice, which consist in giving preference to serum preparations, increase in single and course doses, their multiplicity and duration of administration. Immunotropic drugs of nucleic and native origin as well as combined, complex and immunometabolic correction is primarily applied. Optimal schedules of drug administration are used. They shall be varied depending on the age and the nature of the pathological process. For example, young patients are treated with thymomimetics according to a shortened schedule (3-4 injections), while for older patients a long-term therapy of totally up to 10 injections and more with lengthening of intervals at the end of treatment is applied. If there is a risk of habit formation, the last doses of drugs are decreased up to 1/2-1/4, and in some cases even to homeopathic concentrations. If a patient is diagnosed with liver damage, gastroenterocolitis, drug allergy, etc., prescription of immunomodulators of plant origin is recommended.

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