FEBS 29404 FEBS Letters 579 (2005) 2035–2039

Hypothesis

Inflamm-ageing and lifelong antigenic load as major determinants of ageing rate and longevity

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Received 26 January 2005; accepted 8 February 2005

Available online 11 March 2005

Edited by Barry Halliwell

Abstract Immunosenescence is the consequence of the continuous attrition caused by chronic antigenic stress. The most important characteristics of immunosenescence (accumulation of memory and effector T cells, reduction of naive T cells, shrinkage of T cell repertoire, reduction of the immunological space) are compatible with this assumption. Immunosenescence can be taken as proof that the beneficial effects of the immune system, devoted to the neutralization of harmful agents early in life, become detrimental late in life, in a period not foreseen by evolution. This perspective could explain the mechanisms of the ageing process as well as the pathogenesis of age-related diseases.

Keywords: Antigenic load; Inflamm-ageing; Ageing rate; Immunosenescence; Age-related diseases

1. Evolutionary-based immunosenescence

Immunosenescence is a recent phenomenon, related to the extraordinary and linear improvements in survival and lifespan that began around the 19th century and are still occurring. It is possible to speculate that the role of immunosenescence was indeed negligible in the past, when the human lifespan was 40–50 years, and that its impact on morbidity and mortality has emerged in combination with the extension of lifespan [1]. The changes associated with immunosenescence, such as inflamm-ageing, shrinkage of the T cell repertoire and filling up of the immunological space with memory/effector cells, are playing a more and more important role in the emergence of a series of age-related pathologies, conditioning the present epidemiology of old people [2].

The ageing of the immune system (IS) is not a random process without rules or directions, but rather is subject to evolutionary constraints [3]. The IS has been probably selected to serve individuals living until reproduction. The trend of thymic ontogenesis and involution likely supports this hypothesis [4]. Our ancestors lived until 30–50 years of age. Nowadays, the IS must serve the soma of individuals living 80–120 years, an enormous amount of time longer than that predicted by evolutionary forces. Therefore, old people have to cope with a lifelong antigenic burden encompassing several decades of evolutionary unpredicted antigenic exposure. This chronic antigenic stress and the subsequent inflammatory burden have a major impact on survival and frailty. The quality of ageing and the peculiar remodeling of the IS in more advanced age are the results of the individual immunological history, which therefore heavily influences both longevity and successful ageing [5]. Individual immunological history derives from the interaction between genetic background and specific lifelong antigenic burden [6,7]. This latter depends on historical period where you live, on geography (poor/dirty or reach/hygienized countries) and on social/economic status and education. Indeed, since the genetic pool of humans remained almost constant in the last century, the recent spectacular improvement in survival can be largely attributed to improved life conditions and hygiene [8].

2. Chronic antigenic load

The most important characteristic of immunosenescence is the filling of the immunological space with memory and effector cells as a consequence of exposure to a variety of antigens. The continuous attrition caused by clinical and sub-clinical infections, as well as the continuous exposure to other types of antigens (food, allergens), is likely responsible for the chronic IS activation and inflammation [8,9]. Inflamm-aging, i.e. the peculiar chronic inflammatory status which characterizes ageing, is under genetic control and is detrimental for longevity [10,11]. This age-related chronic inflammatory activity, leading to long term tissue damage, is related to mortality risk from all causes in old persons. A wide range of age-related diseases, such as neurodegeneration, atherosclerosis, diabetes, osteoporosis and sarcopenia, among others, share an inflammatory pathogenesis [12–18]. Therefore, immunosenescence and probably morbidity and mortality will be accelerated in those subjects who are exposed to an extra burden of antigenic load. The phenomenology of HIV+ patients after several years of infection, shows striking similarities (regarding T cell subset derangement, T cell clonal expansion and telomere shortening of T cells) with that observed in aged people [19]. It is possible to speculate that prolonged chronic infections other than HIV, despite being less aggressive, can lead to similar results. Large

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0014-5793/$30.00
doi:10.1016/j.febslet.2005.02.055

clonal expansions of peripheral CD8+ T cells carrying receptors for single epitopes of CMV and EBV, detected using tetramer technology, are common in the elderly and are associated with a loss of early memory cells, an increase of highly differentiated CD8+ cells, a gradual reduction of the immunological space and an immune risk phenotype (IRP) predicting mortality [20,21]. Conversely, immunosenescence will be delayed in those subjects who lived for most of their life in clean environments in which exposure to persistent viral infections and parasitic infections are minimized. This is exactly what happened in the last century in the most economically developed countries in which medical care, vaccination, and hygiene in food, water, and housing contributed to reduce the antigenic load, the exhaustion of naive T cells, the filling of the immunological space, and consequently the rate of immunosenescence [22]. Quality and quantity of the lifelong antigenic load, conditioning inflamm-ageing, is a major determinant of immunosenescence, aging rate and longevity, as well as of quality of life in advanced ages.

3. Oxidative damage

In addition to antigens, other important stressors which continuously impinge on our IS, as well as on the other cells of the organism, are oxidative metabolism by-products, mainly reactive oxygen species (ROS), as a consequence of the lifelong respiratory burst. The increased ROS production and accumulation during ageing induce damage to important cellular components (lipidic membranes, enzymatic and structural proteins and nucleic acids) [23]. ROS damage is counteracted by several genetically controlled enzymatic and non-enzymatic antioxidant defense systems, DNA repair enzymes and specific damage-induced apoptotic processes. All these protective mechanisms tend to become less effective with increasing age and as a consequence cells undergo a sort of oxidative stress adaptation with age-related accumulation of senescent and mutated cells, tissue dysfunctions and increased risk of tumors. The p53 protein works to suppress the development of tumours by affecting how cells respond to damage (DNA repair or, if it fails, apoptosis). The p53 gene also plays an important role in cellular senescence. It appears that increasing p53 activity reduces the incidence of cancer, but concurrently increases the ageing rate. A fine equilibrium between the antineoplastic and pro-aging characteristics of p53 may lead to the optimal lifespan for an organism: too little p53 results in death from cancer, whereas too much p53 leads to death by accelerated ageing. Depending upon the balance of positive and negative influences, cell proliferation can continue or senescence may ensue. Therefore, ageing is an antagonistically pleiotropic manifestation of evolutionary pressures to prevent malignant transformation, perhaps in large part via the actions of p53 [24].

4. Immune system remodeling

The effects of the lifelong antigen stimulation and ROS production on the IS are illustrated in Fig. 1. As a consequence of ROS accumulation, cells become resistant to damage-induced apoptosis and senescent/dysfuntional lymphocytes increase,

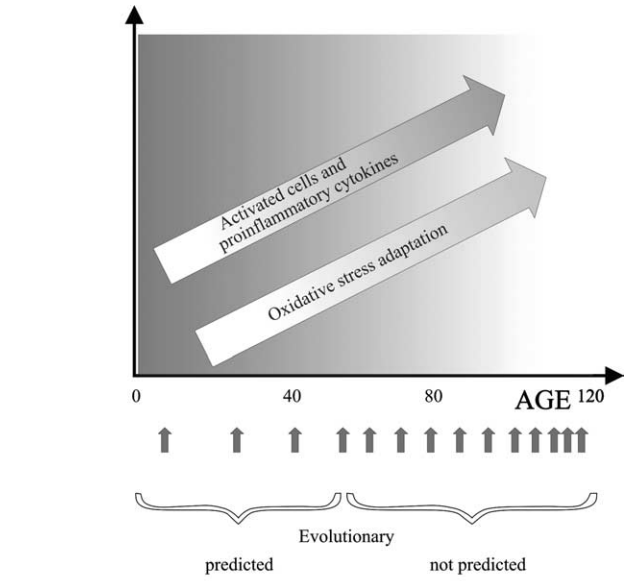

Fig. 1. The continuous attrition on the immune system caused by repeated antigen stimulations (clinical and subclinical infections, food antigens, allergens and self antigens) is responsible for the increase in activated cells and proinflammatory cytokines. As a consequence, a peculiar chronic inflammatory status (inflamm-ageing) characterizes immunosenescence. Inflammation and the continuous production of oxidative metabolism by-products exhert a lifelong evolutionary pressure on the immune system, which undergoes a gradual remodeling in the attempt to re-establish a new balance that assures survival.

whereas chronic antigenic load induces age-related increase of activated immune cells and hyperproduction of proinflammatory cytokines, both contributing to determine IS remodeling and inflamm-ageing [1,10].

The hypothesis of remodeling suggests that immunosenescence is the net result of the continuous adaptation of the body to the deteriorative changes occurring over time. According to this hypothesis, body resources are continuously optimized, and immunosenescence must be considered a very dynamic process [12]. The main findings which characterize the IS remodeling during senescence are illustrated in Fig. 2.

An elderly IS becomes more and more predisposed to chronic inflammatory reactions and is less able to respond to acute and massive challenges by new antigens. A young IS has to cope quickly and efficiently with acute immunological challenges to assure survival and reaching of reproductive age. Such reaction capability gradually burns out because of the lifelong antigenic attrition. Moreover, lifelong antigenic challenges and the increasing antigenic burden, determine a condition of chronic inflammation, with increased lymphocyte activation and proinflammatory cytokines [4].

Another important finding of immunosenescence is the decreased stress responsiveness. The unavoidable chronic overexposure to stressors determines an highly pathogenic sustained activation of the stress–response system leading to a progressively reduced capacity to recover from stress-induced modifications [5,22].

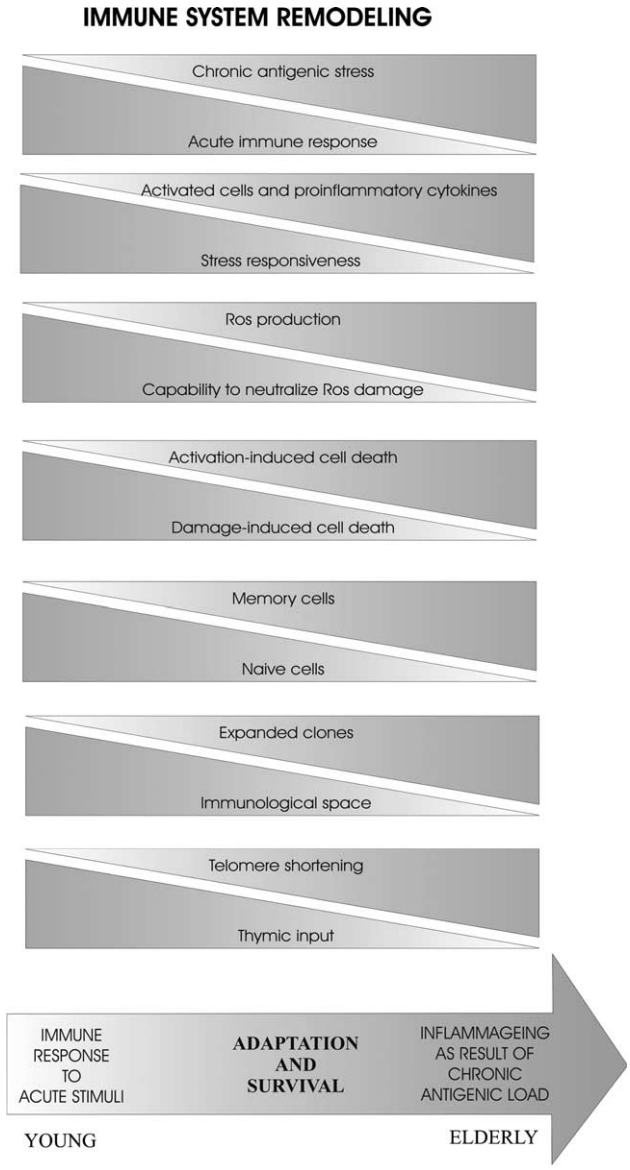

Fig. 2. The main findings which characterize the immune system remodeling, peculiar of immunosenescence, could be interpreted as the result of both lifelong antigenic load and genetically determined ability of the immune system to adapt to and counteract the effects of repeated and chronic antigenic stimuli as well as the accumulation of potentially harmful oxidative metabolism byproducts. In a certain sense, it is the very physiological defense function of the immune system that determines immunosenescence and paradoxically represents the main determinant of the most common age-related diseases and a major determinant of the ageing rate.

ROS are intimately involved with life-span determination, senescence and age-related diseases. Genome instability, driven by oxidative damage, is a primary cause of normal aging [7]. Caloric restriction may extend life-span by attenuating the oxidative stress caused by normal metabolism [1]. Organisms have developed regulatory processes against ROS to implement survival, mainly detoxifying activities, DNA repair enzymes and specific apoptotic mechanisms, which become less efficient during ageing [2]. The correlation between ROS accumulation and oxidative damage on one hand and the rate of ageing and inefficiency of mechanisms protecting from mitochondrial ROS production on the other is extremely good.

As a consequence of both inflamm-ageing and ROS hyperproduction, a subtle modulation of apoptotic mechanisms intervenes during ageing [4]. Lymphocytes undergo two different kinds of apoptotic processes: activation-induced cell death, peculiar of immune cells following antigenic stimulation and clonal expansion, and damage-induced cell death, a more generalized phenomenon in response to a variety of cellular insults, mainly oxidative damage, and is particularly important for preventing the onset of neoplastic proliferation. The decreased sensitivity to damage-induced apoptosis, characteristic of senescent cells, contributes to the accumulation of dysfunctional lymphocytes and expanded clones of memory and effector CD8+ T cells with a global reduction of the immunological space and increased risk of infectious, neoplastic and degenerative disorders. The increase of activation-induced cell death, in response to inflammation cytokines, contributes to exhaustion of naive cells, decreased clonal expansion capability, reduced T cell responsiveness with decreased ability to mount strong immune responses to acute antigenic challenges, and shrinkage of immunological repertoire [5].

The shortage of telomeric DNA is a specific kind of DNA aging used by the cell to count cell divisions and monitor the degree of DNA damage. The progressive increase of telomere shortening, although influenced by genetic factors and telomerase activity, is therefore the result of the individual replicative and immunological history. There is a strong association between telomere length in blood and mortality in people aged 60 years or older [7,25,26].

The thymic input of virgin T cells progressively decreases with ageing. Recently, a marker for newly generated T lymphocytes, possibly related to lymphoid mass, has been identified in the amount of the remnants of T cell receptor rearrangement excision circles (TREC) present in T cells. TREC (similarly to what happens to telomeres) are markers of the T cell replicative history, being progressively diluted by successive rounds of cell division. As expected, the number of TREC drastically decay with age in peripheral blood T lymphocytes [27].

The analysis of immunological changes during senescence and age-related markers of chronic inflammation could provide a window on the individual immunological history as well as useful prognostic markers of morbidity and mortality.

5. Markers of inflamm-ageing

Cellular, serological and genetic markers of inflamm-ageing are now becoming available. On the basis of longitudinal studies [28,29] an immune phenotype predicting morbility and mortality, the so called "IRP", has been defined [12]. The accumulation of antigen experienced T cells is a major characteristic of an aged IS [30,31]. An exhaustion of naive T cells occurs in centenarians [32]. The depletion of virgin CD8+ T lymphocytes can be considered a reliable biomarker related to the risk of death [33,34]. A combination of high CD8+ and low CD4+ T cells and CD19+ B cells, plus a poor T cell proliferation in response to mitogens, is a good predictor of higher morbility and mortality in old people [35].

Ageing is associated with increased circulating levels of pro-inflammatory cytokines. Increased levels of inflammatory

serum markers in the elderly are associated with dementia, Parkinson's disease, atherosclerosis, type 2 diabetes, sarcopenia, functional disability and high mortality risk. Therefore, through inflammation and its mediators the IS influences not only the immunological defence reactions, but also exerts detrimental effects on muscle, bone, cardiac function, haemopoiesis and cognition [15–17]. Furthermore, the production of chemokines (RANTES, MIP-1α, IL-8, MCP-1) is also increased in the elderly, as a consequence of inflammation [36]. Elevated IL6 serum levels are associated with diseases, disability and mortality in the elderly [14,18]. Recent population-based studies identified the magnitude of the IL-6 serum level as a reliable marker for functional disability, and as a predictor of disability and mortality among elderly. Some cytokines, [37–40], for example, IL10 and TNF-α, have complex and predominantly opposing roles in the inflammatory responses. IL10 limits inflammatory responses, whereas TNF-α increases local and systemic inflammatory reactions. Interperson differences in the regulation of IL10 and TNF-α production may be critical with respect to the final outcome of an inflammatory response. The increased production of IL-6 and TNF-α and the reduced production of growth hormone and IGF-I are directly involved in the loss of fat-free mass during ageing. The individual genetic background and the eventual influence of counteracting cytokines could therefore play a determinating role in the onset of age-related diseases. Genetic variations located within the promoter regions of pro-inflammatory and regulatory cytokines could influence inflamm-ageing and the susceptibility to age-related diseases [13].

In conclusion, individuals genetically equipped of strong immunological defence mechanisms and concomitantly characterized by efficient mechanisms for the control of inflammatory reactions, could be potentially destined to become healthy centenarians [41,42]. The lifelong antigenic load and the oxidative stress, impinging upon the IS, configurate the individual immunological history. Longevity largely coincides with successful IS remodeling in response to stressors. Healthy centenarians are therefore those who have the better capacity to adapt to damaging agents and in particular to immunological stressors.

References

[1] Rea, I.M. (2004) Ageing in the 21st century. Where to and how will we get there? Report on the 10th congress of the international association of biomedical gerontology, the geriatrician's view. Exp. Gerontol. 39, 283–284.

[2] Franceschi, C. (2003) Continuous remodeling as a key to aging and survival. Biogerontology 4, 329–334.

[3] Hughes, K.A., Alipaz, J.A., Drnevich, J.M. and Reynolds, R.M. (2002) A test of evolutionary theories of aging. Proc. Natl. Acad. Sci. 99, 14286–14291.

[4] Ginaldi, L. and Sternberg, H. (2003) The immune system in: Physiological Basis of Aging and Geriatrics (Timiras, P.S., Ed.), third ed, pp. 265–283, CRC Press, New York.

[5] Franceschi, C. and Bonafè, M. (2003) Centenarians as a model for healthy aging. Biochem. Soc. Transact. 31, 457–461.

[6] Cooper, R.S. (2003) Gene-environment interactions and the etiology of common complex disease. Ann. Int. Med. 139, 445–449.

[7] Hasty, P., Campisi, J., Hoeijmakers, J., vanSteeg, H. and Vijg, J. (2003) Aging and genome maintenance: lessons from the mouse? Science 299, 1355–1359.

[8] Franceschi, C., Bonafè, M. and Valensin, S. (2000) Human immunosenescence: the prevailing of innate immunity, the failing of clonotypic immunity, and the filling of immunological space. Vaccine 18, 1717–1720.

[9] De Martinis, M., Modesti, M. and Ginaldi, L. (2004) Phenotypic and functional changes of circulating monocytes and polymorphonuclear leucocytes from elderly persons. Immunol. Cell. Biol. 82, 415–420.

[10] Chung, H.Y., Kim, H.J., Kim, K.W., Choi, J.S. and Yu, B.P. (2002) Molecular inflammation hypothesis of aging based on the anti-aging mechanism of calorie restriction. Micr. Res. Tec. 59, 264–272.

[11] Zanni, F., Vescovini, R., Biasini, C., Fagnoni, F., Zanlari, L., Telera, A., Di Pede, P., Passeri, G., Pedrazzoni, M., Passeri, M., Franceschi, C. and Sansoni, P. (2003) Marked increase with age of type 1 cytokines within memory and effector/cytotoxic CD8+ T cells in humans: a contribution to understand the relationship between inflammation and immunosenescence. Exp. Gerontol. 38, 981–987.

[12] Pawelec, G., Ouyang, Q., Colonna-Romano, G., Candore, G., Lio, D. and Caruso, C. (2002) Is human immunosenescence clinically relevant? Looking for immunological risk phenotypes. Trends Immunol. 23, 330–332.

[13] Lio, D., Scola, L., Crivello, A., Colonna-Romano, G., Candore, G., Bonafè, M., Cavallone, L., Marchegiani, F., Olivieri, F., Franceschi, C. and Caruso, C. (2003) Inflammation, genetics, and longevity: further studies on the protective effects in men of IL-10-1082 promoter SNP and its interaction with TNF-α-308 promoter SNP. J. Med. Genet. 40, 296–299.

[14] Roubenoff, R. (2003) Catabolism of aging: is it an inflammatory process? Curr. Opin. Clin. Nutr. Metab. Care 6, 295–299.

[15] Barbieri, M., Ferrucci, L., Ragno, E., Corsi, A., Bandinelli, S., Bonafè, M., Olivieri, F., Giovagnetti, S., Franceschi, C. and Guralnik, J.M. (2003) Chronic inflammation and the effect of IGF-I on muscle strength and power in older persons. Am. J. Physiol. Endocrinol. Metab. 284, 481–487.

[16] Licastro, F., Grimaldi, L.M.E., Bonafè, M., Martina, C., Olivieri, F., Cavallone, L., Giovagnetti, S., Masliah, E. and Franceschi, C. (2003) Interleukin-6 gene alleles affect the risk of Alzheimer's disease and levels of the cytokine in blood and brain. Neurobiol. Aging 24, 921–926.

[17] Abbatecola, A.M., Ferrucci, L., Grella, R., Bandinelli, S., Bonafè, M., Barbieri, M., Corsi, A.M., Lauretani, F., Franceschi, C. and Paolisso, G. (2004) Diverse effect of inflammatory markers on insulin resistance and insulin-resistance syndrome in the elderly. J. Am. Geriatr. Soc. 52, 399–404.

[18] Roubenoff, R., Parise, H., Payette, H.A., Abad, L.W., D'Agostino, R., Jacques, P.F., Wilson, P.W., Dinarello, C.A. and Facchini, A. (2003) Cytokines, insulin-like growth factor 1, sarcopenia, and mortality in very old community-dwelling men and women: the Framingham heart study. Am. J. Med. 115, 429–435.

[19] Appay, V. and Rowland-Jones, S.L. (2002) Premature ageing of the immune system: the cause of AIDS?. Trends Immunol. 23, 580–585.

[20] Valenzuela, H.F. and Effros, R.B. (2002) Divergent telomerase and CD28 expression patterns in human CD4 and CD8 T cells following repeated encounters with the same antigenic stimulus. Clin. Immunol. 105, 117–125.

[21] Ouyang, Q., Wagner, W.M., Wikby, A., Walter, S., Aubert, G., Dodi, A.I., Travers, P. and Pawelec, G. (2003) Large numbers of dysfunctional CD8+ T lymphocytes bearing receptors for a single dominant CMV epitope in the very old. J. Clin. Immunol. 23, 247–257.

[22] Franceschi, C., Valensin, S., Bonafè, M., Paolisso, G., Yashin, A.I., Monti, D. and De Benedictis, G. (2000) The network and the remodeling theories of aging: historical background and new perspectives. Exp. Gerontol. 35, 879–896.

[23] Van Remmen, H. and Richardson, A. (2001) Oxidative damage to mitochondria and aging. Exp. Gerontol. 36, 957–968.

[24] Ferbeyre, G. and Lowe, S.W. (2002) The price of tumour suppression?. Nature 415, 26–27.

[25] Mattson, M.P., Duan, W., Pedersen, W.A. and Culmsee, C. (2001) Neurodegenerative disorders and ischemic brain diseases. Apoptosis 6, 69–81.

[26] Salvioli, S., Bonafè, M., Capri, M., Monti, D. and Franceschi, C. (2001) Mitochondria, aging and longevity – a new perspective. FEBS Lett. 492, 9–13.
[27] Ginaldi, L., De Martinis, M., Monti, D. and Franceschi, C. (2004) The immune system in the elderly. Activation-induced and damage-induced apoptosis. Immunol. Res. 30, 81–94.
[28] Ginaldi, L., De Martinis, M., Monti, D. and Franceschi, C. (2005) Chronic antigenic load and apoptosis in immunosenescence. Trends Immunol. 26, 79–84.
[29] Cawthon, R.M., Smith, K.R., O'Brien, E., Sivatchenko, A. and Kerber, R.A. (2003) Association between telomere length in blood and mortality in people aged 60 years or older. Lancet 361, 393–395.
[30] Saretzki, G. and Von Zglinicki, T. (2002) Replicative aging, telomeres and oxidative stress. Ann. N.Y. Acad. Sci. 959, 24–29.
[31] Effros, R.B. (2004) Replicative senescence of CD8 T cells: effect on human ageing. Exp. Gerontol. 39, 517–524.
[32] Franceschi, C., Valensin, S., Fagnoni, F., Barbi, C. and Bonafè, M. (1999) Biomarkers of immunosenescence within an evolutionary perspective: the challenge of heterogeneity and the role of antigenic load. Exp. Gerontol. 34, 911–921.
[33] Olsson, J., Wikby, A., Johansson, B., Lofgren, S., Nilsson, B.O. and Ferguson, F.G. (2000) Age-related change in peripheral blood T-lymphocyte subpopulations and cytomegalovirus infection in the very old: the Swedish longitudinal OCTO immune study. Mech. Ageing Dev. 121, 187–201.
[34] Wikby, A., Johansson, B., Olsson, J., Lofgren, S., Nilsson, B.O. and Ferguson, F. (2002) Expansions of peripheral blood CD8 T-lymphocyte subpopulations and an association with cytomegalovirus seropositivity in the elderly: the Swedish NONA immune study. Exp. Gerontol. 37, 445–453.
[35] Fagnoni, F.F., Vescovini, R., Passeri, G., Bologna, G., Pedrazzoni, M., Lavagetto, G, Casti, A., Franceschi, C., Passeri, M. and Sansoni, P. (2000) Shortage of circulating naive CD8+ T cells provides new insights on immunodeficiency in aging. Blood 95, 2860–2868.
[36] Mariani, E., Pulsatelli, L., Neri, S., Dolzani, P., Meneghetti, A., Silvestri, T., Ravaglia, G., Forti, P., Cattini, L. and Facchini, A. (2002) RANTES and MIP-1alpha production by T lymphocytes, monocytes and NK cells from nonagenarian subjects. Exp. Gerontol. 37, 219–226.
[37] Brunsgaard, H., Andersen-Ranberg, K., Hjelmborg, J.B., Pedersen, B.K. and Jeune, B. (2003) Elevated levels of tumor necrosis factor alpha and mortality in centenarians. Am. J. Med. 115, 278–283.
[38] Brunsgaard, H., Ladelund, S., Pedersen, A.N., Schroll, M. and Jorjensen, T. (2003) Predicting death from tumour necrosis factor-alpha and interleukin-6 in 80-year-old people. Clin. Exp. Immunol. 132, 24–31.
[39] Cappola, A.R., Xue, Q-L., Ferrucci, L., Guralnik, J.M., Volpato, S. and Fried, L.P. (2003) Insulin-like growth factor I and interleukin-6 contribute synergistically to disability and mortality in older women. J. Clin. Endocrinol. Metab. 88, 2019–2025.
[40] Anisimov, V.N. (2003) Insulin/IGF-1 signaling pathway driving aging and cancer as a target for pharmacological intervention. Exp. Gerontol. 38, 1041–1049.
[41] Perls, T. and Terry, D. (2003) Understanding the determinants of exceptional longevity. Ann Int Med. 139, 445–449.
[42] Troen, B.R. (2003) The biology of aging. Mount Sinai J. Med. 70, 3–22.