ISSN 0006-2979, Biochemistry (Moscow), 2015, Vol. 80, No. 12, pp. 1629-1631. © Pleiades Publishing, Ltd., 2015.
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DISCUSSIONS

Thymic Involution in Ontogenesis: Role in Aging Program

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Received October 1, 2015

Abstract—In most mammals, involution of the thymus occurs with aging. In this issue of *Biochemistry (Moscow)* devoted to phenoptosis, A. V. Khalyavkin considered involution of a thymus as an example of the program of development and further – of proliferation control and prevention of tumor growth. However, in animals devoid of a thymus (e.g. naked mice), stimulation of carcinogenesis, but not its prevention was observed. In this report, we focus on the involution of the thymus as a manifestation of the aging program (slow phenoptosis). We also consider methods of reversal/arrest of this program at different levels of organization of life (cell, tissue, and organism) including surgical manipulations, hormonal effects, genetic techniques, as well as the use of conventional and mitochondria-targeted antioxidants. We conclude that programmed aging (at least on the model of age-dependent thymic atrophy) can be inhibited.

DOI: 10.1134/S0006297915120135

Key words: aging, senescence, thymic involution, phenoptosis, anti-aging medicine

Despite the important role of the thymus as the central organ of the immune system, aging is accompanied by thymic involution in most mammals [1]. Khalyavkin [2] discussed in detail thymic involution as an example of the manifestation of a program of development, and later – control over proliferation and prevention of tumor growth. However, it is known that animals devoid of thymus (e.g. naked mice) are characterized by not only delay and disorders in development and susceptibility to premature aging, but also by stimulation of carcinogenesis [3]. In humans, thymic cellularity and secretion of hormone reaches its peak during the first year of life, and then undergoes many-fold decrease until the age of 50-60 years, and only after that, the rate of decline starts to slow [4]. Thymic involution manifests most dramatically starting from the period of puberty [3]. The biological significance of age-related thymic involution remains unknown. However, it has been shown that it is associated with such a manifestation of age-related changes as insufficient activity of immune cells. Age-dependent involution, in contrast to reversible involutions, is characteristic of all individuals of the given species, although there are clear differences between the genders [4]. The most dramatic decrease in organ parenchyma starts in men aged 25-29 years and women aged 30-34 years. In women, the peak of the maximal decrease of thymic parenchyma is observed at the age of 40-44 years, and in men – at 50-54 years. After the respective decrease peaks, a period of parenchyma recovery begins. This process reaches its peak at the age of 50-54 years in women and 60-74 years in men; then comes an irreversible process of reduction in its content in men and women to the same minimal level (less than 5% of the original value in youth) at the age of 75-90 years [5, 6]. Nevertheless, the function of immunity is well preserved in centenarians [7].

In addition to physiological conditions that change throughout life and control age-related thymus development, random events can cause thymic involution as well as reversible temporal hypoplasia or hyperplasia of the thymus. Rapid reduction of thymic cellularity takes place in young patients who have experienced trauma, chemotherapy, and other forms of stress. Mechanisms that determine the process of involution appear to depend on factors inherent in thymic tissue, such as the local production of cytokines and chemoattractants that promote mobilization, growth, and differentiation of T-cells predecessors in the thymus and on external factors, such as the levels of endocrine hormones and mediators released by intrathymic neurons of the autonomic nervous system [8]. The division of already existing T-cells compensates for reduction in T-cell production, but it leads to gradual domination of memory T-cells and decreased ability to respond to new pathogens and vaccines. It is known that age-related thymic involution in mammals is accompanied by increased sensitivity to infections and many types of cancer [9-11].

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Despite reduced thymic size, release of T-cells to the periphery still occurs in old age, although it is significantly reduced; T-cells of the elderly may accumulate damage leading to the deterioration of the immune system [12, 13]. In case of tumor growth, possible mechanisms of thymic involution are associated with insufficient number of pre-T-cells coming from the bone marrow, enhanced death of lymphocytes in thymus, or their increased transfer to the periphery. It has been shown that glucocorticoid hormones and cytokines such as TNF-α, IL-1, IL-4, TGF-β, and GM-CSF induce thymic involution. It was found that long-term administration of the angiogenic factor VEGF lead to the development of thymic involution similar to that observed in the growth of experimental tumors. VEGF blocking in animals with fibrosarcoma results in the delay of thymic involution [14].

It is assumed that sex steroids facilitate thymic involution [15]. For example, no changes were observed in old (18 months) Wistar rats with no visible thymus seven days after orchidectomy. However, thymus developed 30 days after surgery, although it was smaller than in 10-week-old rats. Histological analysis showed that normal, well-developed vasculature filled with lymphocytes appeared in the tissue; a number of mitoses were also noted [16]. In addition, administration of thyroid hormone causes an increase in the size of the thymus in rats [17], and thyroidectomy results in its reduction [18]. In addition, thymic regeneration was observed in old male Wistar rats receiving a stable analog of the releasing factor of luteinizing hormone [19]. Recently, it was shown that activation of transcription factor FOXN-1 can cause thymic regeneration [20]. Experiments on animals of all ages have shown the possibility of deceleration of thymic degradation due to its transplantation from young animals into the anterior chamber of the eye [9].

Annual thymic involution in hibernating animals is similar to age-related involution of the thymus.

Functional activity of immunocompetent cells in gophers is sharply reduced in autumn; the entire thymic tissue is replaced by brown adipose tissue during hibernation, and a strip of epithelial cells represents it. In spring, the epithelial tissue undergoes the embryonic type of growth followed by lymphocyte infiltration and adipose tissue hypotrophy, which represents a unique mechanism of adaptation. Annual thymic involution is not associated with decrease in ambient or body temperature (it takes place long before the reduction of these parameters); neither is it age-related (it occurs already in the first year of life, also in non-hibernating animals that are bred at room temperature) [21].

It is worth noting that thymic extracts and hormones are used in the treatment (compensation) of age-related degenerative changes [22-24].

For peripheral immune organs, in particular the spleen (the organ that preserves T-cells even after thymus involution and can be easily removed in case of damage without apparent harmful consequences), the situation is more complicated as it is not exposed to marked age-related involution [22, 25, 26]. According to a hypothesis suggested by Makinodan, the number of senescent T-cells increases in spleen with age, leading to autoimmune aging [3]. He administered spleen cells from old mice to young ones and found that the experimental mice had shorter life than the control animals. In addition, vice versa, when cells from young mice were introduced to old ones, these animals were shown to be more resistant to diseases than the control old mice. Makinodan suggested that spleen removal from old animals followed by administration of young functioning T-cells (their own T-cells taken at the young age and frozen or cells from a young donor compatible with the recipient cells) will facilitate significant increase in lifespan [3]. Zuev showed that in case of transplantation of brain or spleen cells from old mice to young ones, the latter undergo accelerated aging. He suggested that the organism of young mice receives (and starts to produce) certain "aging factor", supposedly of protein nature, from donor tissue [27]. A hypothesis on the existence of such substances was stated in the journal *Nature* in 1971 [28]. For example, a single intraperitoneal administration of spleen lymphoid cells from 20-month-old syngeneic mice to 2-month-old mice leads to premature appearance of the aging factor in blood four months earlier than in control [27].

In addition, thymic atrophy has been shown to result from insufficient amount of catalase in stroma, which leads to the increased tissue damage by hydrogen peroxide generated in the course of aerobic metabolism. Genetic introduction of mitochondria-targeted catalase reduces stroma atrophy in C57BL/6 mice similar to chemical antioxidants (N-acetylcysteine or L-ascorbic acid, 15 mg/ml), proving the existence of the connection between antioxidants, metabolism, and normal immune function [29].

Given the involvement of reactive oxygen species in age-related thymus degradation, the development of a new generation of targeted antioxidants seems to be quite promising [29-33]. For example, it has been shown that mitochondria-targeted antioxidant SkQ1 (250 nmol/kg per day) suppressed age-related thymic involution of spleen follicles (where B-lymphocytes are produced) in normal and prematurely aging (OXYS) rats [30]. Thus, we assume that programmed aging can be inhibited, at least in the model of age-related thymic atrophy.

This research was supported by the Russian Science Foundation (project No. 14-50-00029).

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