

REVIEWS

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The Thymus: A Forgotten, But Very Important Organ

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article

Abstract

Medical science seems to be on the threshold of a revolution: It seems possible that in twenty years, doctors will be able to replace organs in the human body like parts in a car. This is thanks to the recent achievement of a team from the Medical Research Council Center for Regenerative Medicine in Edinburgh, Scotland – the group of researchers tried to regenerate the thymus gland in mice. The thymus gland is an essential organ for the development of the immune system, but very few people have any idea that it exists. In the literature and also in people's awareness, the fact is often that the thymus controls and harmonizes the entire immune system and the immune functioning of the organism. It is the primary donor of cells for the lymphatic system, much as bone marrow is the cell donor for the cardiovascular system. It is within the thymus that progenitor cells are created and then undergo maturation and differentiation into mature T cells. The thymus gland is located in the mediastinum, behind the sternum. It is composed of two identical lobes. Each lobe is divided into a central medulla and a peripheral cortex. The thymus is at its largest and most active during the neonatal and pre-adolescent periods. After this period the organ gradually disappears and is replaced by fat. In elderly individuals the thymus weighs 5 g. The aim of this work is to shed new light on this important immune defense organ, whose function is not confined to the destruction of nonfunctional T cells (*Adv Clin Exp Med* 2016, 25, 2, 369–375).

Key words: thymus, thymocytes, thymosin, thymus regeneration.

The media regularly bombard us with sensational news about the results of cell culture research. In 2014, researchers from the Center for Regenerative Medicine in Edinburgh, Scotland, managed to grow a new organ in a living organism for the first time. The research group collected embryo cells called fibroblasts derived from mice and reprogrammed them so that they changed into thymus cells. The cells changed shape and acquired the ability to produce T-lymphocytes. The Scottish researchers not only managed to start the process of re-growth of the thymus in adult mice, which functioned and looked like a typical thymus, but also restored a natural mechanism which normally weakens with age. They focused on the FOXP1 protein secreted by the cells of the thymus gland, which controls the activity of certain important genes. Increasing the level of FOXP1 led to gene activation, which resulted in stem cell transformation into thymus cells. The most specta-

cular thing is that this renovated thymus resumed normal function and began to produce T-lymphocytes, which are of great importance in fighting infections [1].

The Scottish researchers do not yet know whether the regeneration of the thymus led to actual improvement in the immune system of the mice; this will be tested in the near future. They have great hopes that a similar mechanism could be possible in patients with thymic disorders or in elderly people with weakened immune systems. The new approach offers many possibilities in regenerative medicine. If similar procedures prove to be effective with other internal organs, it would mean a real revolution in medicine.

The name of the thymus gland is derived from the Greek word θυμός (*thumos*), which means "soul", and for centuries it was believed that the soul was localized in this part of the body. Galen was the first who noted that the thymus diminishes

as the organism ages [2]. The thymus grows from birth to 2–3 years of age, then it reaches its highest weight (30–40 g), and then begins to shrink in the period of adolescence (because of the influence of sex hormones present in the bloodstream). Its proper functioning during childhood ensures that the immune system is in good condition [3].

Scientists and researchers were trying to understand the function of the thymus for centuries. The presence of a large mass of tissue in children was not appreciated until the moment at the beginning of the 20th century when autopsies of infants who had died of diphtheria showed the presence of a small thymus [4]. Previously, a small thymus had been considered to be the norm.

When an infant's death occurred during anesthesia, an overgrown thymus was considered the cause of it, not the anesthetic. To reduce the size of the thymus, radiation therapy was even prescribed by some doctors, who did not realize that the effect of such treatment could be adenocarcinoma of the thyroid [5].

Until 1961, the thymus was not thought to play any role in the regulation of the immune system. In contrast to cells derived from the spleen or lymph nodes, thymic cells showed a poor ability to initiate immune reactions after transfer to an appropriate cell growth medium. Also, studies performed *in vivo* in mice found no documented immune response defects in mice following thymectomies. These facts lead to the conclusion that "the thymus is not involved in the regulation of immune responses" [6].

Jacques Miller wrote: "At a symposium on Cellular Aspects of Immunity, published in 1960, in which world-renowned immunologists including Burnet, Good, Lederberg, Medawar, and Mitchison took part, not a single reference was made to the thymus or to its cells" [5]. Immunologists found that the thymus is responsible for the neutralization of nonfunctional T cells. Medawar said: "We shall come to regard the presence of lymphocytes in the thymus as an evolutionary accident of no very great significance" [5].

At the end of 1950, Jacques Miller performed a clinical study in mice with lymphocytic leukemia, caused by injection of filtered extracts from a patient's tissue. Leukemia virus is considered to be the causative agent of the disease, which is why newborn mice were injected. The disease originated from the thymus, and a thymectomy performed in the first month of age prevented the disease [6]. One possibility was that the virus can reproduce only in the neonatal thymus. To test this, the thymus was removed from mice shortly after birth, prior to the implantation of the virus. These mice grew well at first, but later many of them died prematurely, regardless of whether or not the virus was

inoculated. The author's conclusion was that "the thymus after birth may be necessary to life" [7].

Thymus histopathology of mice that have undergone thymectomy showed a marked deficiency of lymphocytes in lymphoid tissues and liver damage indicating a hepatitis virus infection [6]. Gowans et al. showed that small lymphocytes are not short-lived cells as previously thought, but immunologically competent cells of with a long lifespan that can recirculate between the blood and the lymph. Moreover, Gowans et al. proved that small lymphocytes are able to initiate immune responses after antigen stimulation [8].

Of course, mice that had undergone thymectomy showed increased susceptibility to viral infections. Therefore, their immune competence was tested by transplanting allogeneic skin of mice and rats to mice with a deficiency of T cells after the removal of the thymus. The results were spectacular: No skin graft rejection occurred, either from unrelated donors (with compatible HLA) or from the rats. Taking into consideration the previous conclusions of Gowans and Medawar, who had proved that lymphocytes are responsible for the process of skin graft rejection, it was logical to conclude that the thymus is a source of immunocompetent cells, at least in the neonatal period [9, 10].

Jacques Miller was the first who postulated, contrary to previous opinions, that "[d]uring embryogenesis the thymus would produce the originators of immunologically competent cells, many of which would have migrated to other sites at about the time of birth. This would suggest that lymphocytes leaving the thymus are specially selected cells" [10]. Miller postulated that the thymus is responsible for the maturation and selection of immunologically competent small lymphocytes [11].

Neonatal mice that have undergone thymectomy showed a deficiency of small lymphocytes [12]; this was the reason for their defective immune reactivity. However, mice whose thymus was removed in adulthood also showed a decreased population of small lymphocytes, but no abnormalities of the immune system were noted [13]. These data suggest that a reduction in the total number of small lymphocytes may be the element responsible for immunodeficiency in newborn mice.

The Effect of the Thymic Hormone on Thymocyte Competence

It is well known that small lymphocytes are the cells responsible for defending the organism against foreign antigens circulating in the blood [14], and

it seems reasonable to postulate that thymosin has a direct effect on the cells that are involved in immune reactions. The mechanism of thymosin's action may be explained either by stimulating lymphopoiesis (Metcalf proved that the thymus produces a cell-stimulating factor [15]), or by the induction of immune cell competence. Thus, the lack of an immune response by lymphocytes from the thymus can be explained by the fact that the cells leave the thymus before achieving a fully mature immune response. However, their subsequent development taking place outside the organ is still under the influence of thymosin. In this process cells undergo a subsequent step, during which they reach their full ability to initiate an immune response. Contact with an antigen stimulates mitotic activity, which results in the cloning of cells capable of neutralizing the antigen. Contact with an antigen also causes an increase in lymphopoiesis in the peripheral lymphoid organs [16]. A neonatal thymectomy removes not only the source of cells that become part of the peripheral lymphoid organs, but also the environment for the functional maturation of lymphocytes. Therefore, those cells that left the thymus just before thymectomy in newborn mice remain locked in the same stage, without the possibility of achieving the immune competence. Providing the thymus hormone, either naturally by diffusion from the thymus or by taking thymus biopsy from an unborn mouse fetus, would allow the maturation of thymocytes to complete. But because neither of these theoretical methods would result in a greater number of thymocytes, there would still be a paucity of cells in the lymphoid organs and in the circulation. Further experimental studies are needed to confirm the above hypothesis.

The Role of the Thymus in Clonal Selection of T-Cells and the Elimination of Self-Reactive Clones

T-cells can recognize foreign antigens. Thanks to this capability T-cells can maintain homeostasis. More than 95% of T-cells are destroyed by apoptosis. The trigger signal is a positive T-cell response to self-antigens presented by the major histocompatibility complex (MHC) system. Clonal selection means that only those cells that can recognize the antigen are activated. The result of this activation is the secretion of antibodies and mitosis of T-cells, resulting in increasing quantities of T-cells recognizing the antigen. This is an immediate response

to a pathogen [17]. When the pathogen is eliminated, the activated cells undergo apoptosis, and only a few survive as memory immune cells. Thanks to this, the memory cells are more numerous than before and the subsequent response is even faster and more effective. The thymus also plays an important role in the mechanism of central self-tolerance. Central tolerance is mainly based on clonal deletion of self-reactive T-cells. It takes place during the maturation of immune T-cells and relies on so-called "positive selection", in which only those T-cells survive that do not react with the self-antigens. The thymus is also responsible also for negative selection of the lymphocytes that bind with high affinity to the antigen; these are eliminated by apoptosis. Apoptosis is "programmed cell death", and it plays a very important role in the selection of thymocytes in the thymus; it is also the way auto-reactive clones of T-cells in peripheral blood are eliminated [18].

Involution of the Thymus

One of the most important factors contributing to the reduction of the immune response with age is the phenomenon of involution of the thymus. As an individual ages a gradual decrease in the structural integrity of the thymus can be observed. This process contributes to a steady decline in the production of undifferentiated T-cells, which leads to a limited repertoire of TCR cells. Since some of these cells are turned on in the immune memory cells (because of the constant stimulation of the antigen) there is an increased risk of severe infections due to the scarcity of naive T-cells. The development of the thymus takes place during gestation, and the organ attains functional maturity in the perinatal period. After that the thymus's functions gradually decrease with age. The overall size of the thymus in adults is much smaller than in children, whereas the amount of non-functional tissue is much higher. This is accompanied by the loss of the organized architecture and increased fat cell deposition in this organ [17]. There are several possible explanations for this involution, such as the scarcity of T-cell precursors from bone marrow, the effects of circulating hormones and cytokines, or the loss of thymic architecture with age [18]. However, none of the theories explains with certainty why thymus function decreases with age, since undifferentiated T-cells are also needed in adult life. There has also been an attempt to explain thymic involution as a part of the evolution of this organ. The results of a clinical study by Ma et al. [19] may provide evidence for this hypothesis; in this study, chemical or sur-

gical castration of male mice lead to a decline in sex hormones and inhibited age-related thymic involution. What's more, the administration of androgens and estrogens to uncastrated mice resulted in reduced thymopoiesis. The interpretation of this experiment in relation to humans is difficult, because human thymuses have full functionality immediately after birth and the decay process begins in the first year of life, long before puberty [19]. In mice, however, the time between weaning and reaching sexual maturity is not long, and it coincides with the beginning of thymic involution. Furthermore, the reduction in androgen levels that occurs with age in humans shows no correlation with the reversal of thymus involution. These arguments indicate that the levels of sex hormones may affect the process of thymus involution, but are not the only factors responsible for this phenomenon. T-lymphocyte progenitor cells and thymic epithelial cells remain in constant mutual communication and are interdependent. There is a qualitative decline in the production of precursor cells with age [19].

Thymus Hyperactivity

Thymic hyperplasia associated with overactivity is also possible. Most often it occurs in myasthenia gravis, but also in endocrine disorders such as hyperthyroidism. Also, tumors of the thymus (thymomas) may be the cause of the growth of the organ and cause endocrine disorders like hyperadrenocorticism. The clinical picture is characterized by hyperactivity of the thymus: pale skin, lymphatic node hyperplasia, tonsillitis and rhinitis. The treatment consists of administration of iodine, vitamin A, vitamin D and calcium; thalassotherapy, heliotherapy and thymus region radiotherapy can be applied [20].

The Consequences of Thymus Disorders

Small thymus size in preterm newborns leads to infections. A clinical study involving newborn preterm babies showed that there is a correlation between small thymic size and higher mortality in the first year of life because of infectious disease [20]. Extreme prematurity is related to increased susceptibility to infectious illnesses and decreased infant growth. These findings may indicate that extreme prematurity might lead to a smaller thymic size and can influence immune function.

Immune deficiency is the cause of many diseases – not only recurrent and chronic respiratory in-

fections, but also a large number of diseases of other systems, for example diseases of the genitourinary tract, skin and mucous, autoimmunity syndromes such as multiple sclerosis, systemic lupus erythematosus or thyroiditis [21]. Very few people realize that the process of aging correlates with a decreased ability of the immune system to generate antigen-specific responses to pathogens and vaccinations [22]. This results in a higher frequency of infections and autoimmune diseases. The probability of tumor growth increases with age, as observed in the elderly and immunosuppressed. These profound changes are due to aging of the immune system, which is referred to as “immuno-aging”. It impairs both innate and acquired immunity [23].

The thymus is an organ sensitive to stress, alcohol, cigarettes and drugs of any type. All of these can cause hypertrophy. Thymus hypertrophy often accompanies myasthenia gravis, defined as muscle fatigue, an autoimmune disease that leads to skeletal muscle weakness. Antibodies produced in the thymus, combining with acetylcholin receptors, interfere with proper signaling between the nervous system and muscles [24]. Also, other autoimmune diseases, such as systemic lupus erythematosus or hyperthyroidism, may cause thymic hyperplasia. Other causes of thymic hyperplasia may be neoplastic, such as thymomas and lymphomas [24].

Thymus hypertrophy is observed in the majority of people suffering from myasthenia gravis [24]. Therefore, an essential element of diagnosis, in addition to immunological tests for the presence of antibodies AChR and anti-MuSK, is a chest CT or MRI scan to assess the size of the thymus [25].

The role of the thymus in myasthenia is still not fully understood. Some studies suggest that thymus lymphocytes are “sensitized” for elements of muscle cell membrane [26]. Mature lymphocytes recognize acetylcholine receptors present on the surface of membrane as “foreign” and stimulate the production of antibodies. These, after reaching the neuromuscular junction, block these receptors, preventing access to acetylcholine and the signal transmission. The disease progress varies between individuals, with periods of exacerbation and remission. Treatment depends on the severity of the disease. In most cases immunosuppressive drugs and corticosteroids weaken the aberrant activity and modulate the immune system [25]. Frequently, the success of drug treatment is dependent on a surgical thymectomy. In some patients, the only treatment necessary is pyridostigmine bromide, which slows the breakdown of acetylcholine. It is also important to avoid drugs that cause exacerbation of the disease. The list is long and includes

substances used in the treatment of various illnesses, including antibiotics, anesthetics, ophthalmic and cardiac medications [26].

Atrophy of the thymus is also pathological; it can be observed in congenital syndromes. One of them is the Di George syndrome, in which the decay takes place *in utero*, resulting in cellular immune deficiency and greatly increased susceptibility to infection [27]. Another congenital disease is severe combined immunodeficiency (SCID) – a genetic disease involving a lack of T and B lymphocytes; in this case thymus gradually disappears [28].

Starting in the 1970s, many attempts were made to develop thymic hormone replacement therapy as a first step toward a new approach to the treatment of a number of serious diseases. The end of the 20th century brought a decline in therapy aimed at reconstructing damaged structures and functions of thymic hormones, but that was a transient state of affairs. In just the last six years more than 500 works have appeared around the world about clinical applications and pharmacodynamics of thymus preparations. Further research to verify the effectiveness and safety of these preparations is still underway.

Thymus Transplantation

The thymus is sometimes removed, for example in patients with thymoma, raising concerns about the lifelong impact of thymectomy. Residual thymic function or thymic regeneration might be sufficient to re-establish the host's defense [29]. If necessary, the thymus itself is sometimes transplanted, to establish immunity or to generate tolerance [29]. This is a promising procedure to ensure immune system reconstitution after immunosuppressive interventions and to modulate T-cell tolerance.

Researchers at Duke University Medical Center (Durham, USA) have performed numerous successful thymus grafts on children with DiGeorge syndrome. As of 2010, the team there had “performed thymus transplants for 26 infants with complete DiGeorge syndrome, including (...) six who received the new immunosuppression treatment” [30].

Creating an *Ex Vivo* Thymus Gland

Attempts to create new thymus glands originated from the awareness that this organ is essential for the human immune system. The idea was to create an organ from undifferentiated fibroblasts that transform into thymocytes [31].

The existence of thymic epithelial precursors has been demonstrated in the mouse embryo, with a single thymic epithelial precursor cell able to differentiate into both cortical and medullary precursors of T-lymphocytes. There is evidence that progenitors of T-cells exist in the post-natal thymus that can differentiate into both cortex and medulla cells [32].

Clark et al. showed that human skin keratinocytes, together with mesenchymal fibroblasts and exogenous growth factors, can support the development of functional “self-tolerant” T-cells. Their research supports the possibility that an *ex vivo* thymus can be produced [33]. However, for any clinical relevance, it is essential to isolate thymic epithelial cell precursors from a human thymus.

The idea was to develop a new method for the regeneration of the thymus in elderly patients with immune disability in order to improve the quality of life [34]. Progenitor cells were obtained from thymus tissue removed during surgery on congenital heart defects. New biotechnology procedures were performed to obtain non-immunogenic T-cells in the treatment of 70-year-old patients whose central immune system did not function properly. As a result of the *in vitro* process a human thymus gland capable of regenerating the human immune system after transplantation was created for the first time; previously it had been achieved only in animals [34].

An old thymus lowers resistance to infections in elderly people. Damage to the thymus gland in the patients who have undergone bone marrow transplantation also affects the immune system. Both of these groups comprise a significant part of European society. The Thymistem initiative, led by the University of Edinburgh, is working on achieving the goal of restoring the function of the immune system by transplantation of thymus cells [34]. The results show that thymus cell transplant may be an effective way to repair the immune system and restore functionality, but the main obstacle is a lack of sources for these specialized cells. Cells derived from adult donors do not have the same effect, as the gland disappears with age. The Thymistem team, with scientists from the Center for Regenerative Medicine (CRM) at the University of Edinburgh, is going to deal with this problem by using new methods of producing thymus stem cells in a laboratory that will serve as an alternative source of cells for the purpose of therapy [35].

CRM scientists have succeeded in “reprogramming” mouse embryo cells. They combined them with helper cells and transferred into a different mouse, where transformed into a functioning thymus, with a typical construction of cortex and stem, ready to produce T-lymphocytes. According to the study authors, cultivating a patient's organs

in the body could become an alternative to transplantations. It would be possible to help children born without a thymus, as well as elderly people. But before that happens, more research is needed to exclude uncontrolled proliferation and neoplasma formation [35].

Conclusions

The results of studies on mice described in this review paper undoubtedly lead to the conclusion that the thymus (although it undergoes involu-

tion), is an organ of great importance, responsible for the processes of tolerance, immune reactivity and the production of immunologically competent T-cells. Thymus dysfunction leads to serious disturbances in the body's defense mechanisms, and thymus hyperactivity results in serious diseases, both autoimmune and proliferative. Without this organ, the human organism does not have a properly functioning immune system. If the thymus functions properly in childhood, the immune system develops the mechanisms responsible for fighting infections. However, if it is damaged in infancy or childhood, immunity remains impaired.

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