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Microarchitecture of the Thymus Gland; Its Age and Disease-Associated Morphological Alterations, and Possible Means to Prolong Its Physiological Activity

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Abstract

Thymus is a ductless, highly organized, bilobed encapsulated gland of the lymphoid organs that contributes in thymopoiesis. Thymus plays an important function in the assortment, progress and profusion of T cells. The mature subsets of thymus dependent lymphocytes linked with the thymic epithelial and other cells developed the microstructure that protect the body from the harmful foreign micro-organism. Most of the thymic lobular areas experienced the parenchymal cells hypoplasia, undergone infiltration of stromal FCT and experienced thymic atrophy with age progression. As the host gets adult, the regression of the thymus and the thymopoiesis occurs, which ultimately boost the vulnerable situations of the host and open a gateway to autoimmune diseases. Since past decades, scientists are intensely investigated to develop some tactics for the improvements of the thymus performance including T-cell regeneration and maturation with age progression. This unique organ is continuously altered morphologically with age and disease; however, this microarchitectural alteration and its possible modulations is not yet clear. Therefore, the main purpose of this chapter is to highlight the micro-structural compartments and physiological modification of the thymus with age. Also, the chapter is suggesting the possible alternative ways to improve its durable physio-morphology in vertebrates.

Keywords: thymus lobules, histophysiology, lymphocytes, atrophy

1. Introduction

Thymus gland is a primary lymphoid organ, situated in thoracic cavity, ascends from the endodermal layer of the third pharyngeal pouch of the embryo. Based on same origin, thymus can be linked with that of the parathyroid, but during embryogenesis it is separated from that endocrine gland [1]. Thymus faced the process of evolutionary atrophy with age in almost all the animals which leads to the architectural alterations [2]. Its anatomy is variable among species. In new-born fowl, its color is greyish pink and has two left and right lobes. It is ventral to the trachea and the large vessels, but its lobules may prolong up toward the thyroid gland.

Thymus gland in dog is a compressed bilobed structure located in the cranial mediastinum that is laying cranial to the heart and behind the sternum. Its size is largest in young which is followed by atrophy with the age progression until only a trace remains [3]. When it is fully developed, its caudal part is melded on the cranial surface of pericardium. Divisions of the inferior thyroid, internal thoracic arteries, and superior thyroid artery supply blood to the thymus. These arteries travel along the connective tissue septa, which is extended from the covering capsule into the thymic parenchyma [2]. Histologically, however, it is an old technique, but it is still used excessively in the medical field for the understanding of the organ's microarchitecture [4]. The septa divide the parenchyma into small incomplete microscopic lobules, Where they entered the thymus gland. Veins, inferior thyroid, internal thoracic and left brachiocephalic vein takes blood away from thymus gland. Nerve supply of the thymus gland arises from the sympathetic nerves of the cervical chain and the vagus nerve. Extended divisions of the phrenic nerves stretch up to the covering capsule of the thymus but are not arrive to the gland parenchyma [3]. The function of such enervations to the thymus gland is not well comprehended. Lymphatic vessels drain into the lymph nodes viz. parasternal, tracheobronchial, and brachiocephalic. Histologically, the thymus gland appears as a lobulated lymphoid organ, enclosed with a capsule, made up of a fibrous connective tissue (FCT). Capsule surrounding the organ have blood vessels which supply blood to the thymus gland parenchyma. The CT-composed trabeculae descended downward from the capsule, splits the thymus parenchyma into many incomplete lobules by extending into the interior of the organ [5]. These lobules consist of the following two parts: the cortex is a dark staining outer region just beneath the FCT capsule. It contains densely packed lymphocyte that is not involved in the formation of lymphatic nodules. This portion support the early thymocyte development also positively selects the major self-histocompatibility complex. This portion is very thick at the earlier age. The junctional point between the two compartments is called as corticomedullary junction. This is the specific area where the thymic precursor cells enter in the adult age and few of them differentiate into NK cells and the dendritic cells later few reached to the subcapsular sinuses. This corticomedullary area is also very clear and become blurting and even more fuzzy with the progression of age [6]. The medulla is a light staining inner/central region. Medulla contains later thymocyte differentiation to subpopulation like CD-4 and CD-8, also have fewer lymphocytes than cortex but have more epithelial reticular cells. It also has many thymic (Hassall's) corpuscles which differentiate it from other lymphoid tissues/glands [3]. The Hassall's corpuscles are variable sized ovoid structures composed of granule cells, epithelioid cells, and concentric layer of reticular cells containing keratohyalin and eosinophilic fibers. Under microscope the Hassall's corpuscles and the bubble-shaped adipose tissue appears in the area and their number increases with the age progression [7]. Medulla also shows the continuity between the lobules, because the lobules are incomplete. Thymocytes mature, downregulate, and reach the medullary regions.

Cellular components of the thymus glands comprise of emerging thymus-derived T cells (later population reached to 95%), the stromal cellular system including the microvasculature, the mesenchymal cells, the dendritic cells, and the very important thymic epithelial cells (TEC) [8]. Few macrophages are present in almost all parts of the gland but in medulla it plays important role in the apoptosis. The TEC are categorized into three key classes including cortical, medullar and subcapsular/perivascular based on localization in the thymic parenchyma. The dendritic cells are mostly found in the corticomedullary junction and in the medulla. All the aforementioned cells participated in the thymocyte function started from the receiving of the progenitor cells till its final training and maturation. During the period of advance gestation, the thymus in the fetus has unclear cortex and medullary regions,

contains differentiating T cells, macrophages along with B cells and a developed CT capsule with the vasculature connection [9]. Soon after birth, the thymus develops altogether along with the cellular compartments. In the aged individuals, the involution of the thymus is initiated, which is easily seen in the histological sections in the form of thinning of the cortex as well as the haziness of the corticomedullar junctions. Thymic epithelial cell proliferation is a key player in the development of the thymus in the infant [5]. Recently, the hyperplastic proliferation of the thymic epithelial cells was observed in the transgenic lab animals. Thymic fragments of the neonates and that of the bone marrow transplant to the adult individual is also observed experimentally. It has been suggested that stem cells have the capacity to differentiate and develop the organ system of the same kind cells [10]. The progeny of the stem cells may develop the tissue directly or may differentiate into a new stem cell. It is possible to grow the stem cell in vitro, and it is needed to support these cells in the living individual. It would be a big achievement in the science, if the stem cells could possibly grow and could differentiate into the thymic cells in the thymus parenchyma like those present in the intestinal crypts, skin, and liver. In this chapter, we will focus on our current understanding about thymus architectural modulations in health and disease and its possible physiological improvement.

2. Physiology of thymus gland

Major role of the thymus gland is the training of variety of T cells that respond to the antigens. Its function is mainly regulating by the response of the cytokines and for this the equilibrium among anti-inflammatory and proinflammatory cytokines of the body is crucial. It has been observed that thymic atrophy is associated with age linked with diminished interleukin-7 expression [6]. Thymic epithelial cells are originated from a mutual bipotent ancestor and are also the main constituents in the growth of T cells in the thymic microstructure. It comprised of the two regions including the cortex TECs which is positioned in the cortical regions and the medulla TECs which is in the internal medulla. They experience a sequential progress which is organized by various signals, which later leads to support in physiological maturation and development of the thymocyte. The TECs playing a role in the selection of T- cells in the thymus parenchyma [5]. Both cortical and medullar TECs play distinctive responsibilities in the positive and negative selections of the thymocyte.

3. Differentiation, proliferation, and development of lymphocytes

The undifferentiated lymphocytes are migrated from the reservoir, that is, bone marrow to the thymus gland by means of blood stream. The thymic cortex contains the reticular cells, also known as thymic nurse cells. These cells surround the lymphocytes and enhance the differentiation, proliferation, and maturation of the cells [11]. The lymphocytes get matured and get transformed into immunocompetent cytotoxic T cells, helper T cells, and the T cell. At this stage, the receptor is being attached at surface of the lymphocytes for the recognition of antigens. This process starts just before the birth and continues till some month after the birth. Almost 1% of the mature lymphocytes are getting out of thymus toward the margin on daily basis. The differentiation and further activations of T cells to CD-4 and CD-8, and then established T cells travels from thymus to the marginal blood vessels and secondary immune organs [9, 11]. Thus, the size and mass of thymus reflect the maturation of the immune system.

4. Blood-thymus barrier

It is a physical barrier formed by endothelial cells, epithelial reticular cells, and macrophages. Its function is to prevent developing lymphocytes from the exposure of blood borne antigen [8]. This barrier provides tremendous environment for the substance exchange between vasculature and the thymus also help maturation of the immature thymocytes. Macrophages present outside the capillaries prevent the interaction of the substances that are transported in the blood vessels with the developing T cells in the cortex. Matured T cells leave the thymus gland through the blood vessels and colonize in the lymph node, spleen, and lymphatic tissue of the organism [11].

5. Maturation and selection of T cells

Maturation is the condition of developing progenitor within the thymus parenchyma, where the cells known as thymocytes, undergoes various developmental processes to perform exclusively. These cells can be recognized based on manifestation of various markers on the cell surface and the antigen presenting cells present the T cells with self and foreign antigen [11]. It usually consists of positive selection in which the lymphocytes that recognize the foreign antigens survived and reached to the maturity then enter the medulla through the cortex. Later, goes to the other sites in the body via blood [9]. Maturation is a very complicated process and only a small number of lymphocytes reach to the stage of maturity in the thymus. The negative selection in which the lymphocytes which are incapable to distinguish the self-antigens are eliminated by the macrophages. This is approximately 95% of the total cells.

6. Function of epithelial reticular cells

Epithelial reticular cells, also called as TECs, are present both in the cortex and medulla; however, it can be easily recognizable in the thymic medulla through histology. These cells contained the thymic granules which is assumed to be the called as the thymic hormone [12]. This structure has the following functions;

- It formed the blood-thymus barrier.
- Secrete hormone which are required for proliferation, differentiation, and maturation of T cells. Also, for the expression of their surface markers. The hormones including thymulin, thymopoietin, thymosin, thymic numeral factor, interleukin, and interferon are secreted.
- It forms thymic (Hassall's) corpuscles, distinctive whorls, in the medulla of the thymus gland. The thymus gland is identified by this thymic corpuscle.

The pluripotent progenitor cells migrated from the bone marrow to the thymus parenchyma, where the maturation of the unexperienced T cells occurs in the complex microarchitecture. However, this structure changes with the age.

7. Age associated changes occurs in the thymus

Aging is an irreversible, on-going, and inevitable progression that is correlated through manifold organ dysfunction. The key organ of immune system and

primary organ of T cell production is the thymus gland which is endodermal in nature. Involution of the thymus with progressing age is into the consequences of a decreased T cell production primarily and leads toward a long list of the following diseases and even a mortality of the individual [6]. The corticomedullary junction is disrupted and the number of medullary epithelial cells are also decrease. This age-related cellular apoptosis and atrophy is still un-answered. There are several reasons to be considered for this process, but the main cause known is reactive oxygen species (ROS). The entity that are assumed to be responsible for expressing the age-related changes in the thymus is due to the discrepancy amongst the free oxygen-derived radicles and that of the antioxidants. Mitochondria is the main site where such reactive species are produced. Inside mitochondria, the oxidative stress produce ROS which results into mitochondrial damage within the cells and leads to liberate more ROS. In fact, aging is a physiological multifactorial process accompanied by decline of organ function. Histologically, the thymus gland of mammals divided into three consecutive morphological stages; the epithelial, the lymphopoietic, and the differentiated cellular microenvironment [7]. The progenitor cells are synthesizing in the thymus which later differentiated into mature T cells. Thymus also comprises the main stromal niche termed as thymic epithelial space. It supports T cell development and maturation [6]. The thymus is greater in size and is very dynamic in the neonates and pre-adolescents. With the progression in age, the involution starts and ultimately disappears and are then replaced by rudiments and fat. The process of involution started just after 1 year of birth [2]. If in case the thymus is absent in individual congenitally, then there would be a probable chance of deficiency of T cells. The main components of the thymus which undergoes involution during the aging include the T cells of hematopoietic origin and the TECs of non-hematopoietic origin. During the process of involution, disruption of the thymic epithelial/endothelial ratio happened and results into gradual loss of pro-T cells. Primarily just after the start of involution, the thymic epithelium mass is decreased in the parenchyma. This decrease in epithelium leads toward the disorganization of corticomedullary junction and results into loss of demarcation between the thymic cortex and medulla. This process where a continuous loss of cells and their functions is called aging [6]. Histology of thymus gland varies with the individual's age. It is observed that this gland is extremely delicate to stand against the biological abnormalities, for example, autoimmune diseases, infection, and age progression. It attains its maximum development shortly after birth. After attaining the age of puberty, the thymus gland regress and degenerate. Due to this effect the lymphocyte production decreases and the reticuloepithelial cells (thymic corpuscles) increases. Cellular portion, especially of T cell of thymus gland, decreases and are being replaced by connective tissue and adipose cells. Parenchyma of the thymus gland at and after puberty is filled with adipose tissue. Immunity, however, in this stage it is not compromised because progeny of the T lymphocytes has already been established. Thymus gland is well developed only in late fetal life and persists for a few months after birth [6]. Subsequent to this period, it undergoes rapid atrophy, fatty infiltration, and the amyloid degeneration [13]. Increase in the amount of adipose tissue and fat-bearing cells in the thymus parenchyma indicates that the body is now vulnerable to the infection and autoimmune diseases. So, in adult, only a thin remnant appeared in the anterior mediastinum or has entirely disappeared. Thymus gland size is also affected by the sex-steroid hormone and hypothalamic-pituitary-adrenal axes hormones [14]. It has been found that during the thymus involution, the CT which is present in the capsule, septa, perivascular tissue, and in the stroma of the cortex and medulla is getting enriched with the fibronectin contents. Later, most of the thymic parenchymal areas are being replaced by the stromal cells.

8. Effect of removal of the thymus gland and its clinical significance

Thymus gland is an important component of immune system. This system defends the host from several infections [11]. It's inappropriate performance may produce embarrassment or even fatality. If the thymus gland is removed from the new borne individual, then there will be no possibility of the T cell production [6]. Other, lymphoid organs will also lack or decrease the number of T cell to fight against the pathogens. Consequently, death of the individual may occur, predominantly due to complications with infection and lack of immunity.

9. Effect of malfunctioning thymus gland on the body

Thymus experiences atrophy with time which is triggered by numerous factors viz. growth and aging, infections and endocrine instabilities which give rise to a nonstandard liberation of T cells and consequently weakened the immunity [6]. The main organic task of this gland is to spawn a distinct T cells range to establish a crucial portion in host immunity counter to external pathogens, whereas the thymus correspondingly theaters a serious part in self-tolerance through negative assortment and the T reg cells formerly known as suppresser T cells production. Some of the thymic-derived malfunctionings are categorized bellow.

9.1 Hypersensitivity/immunodeficiency or autoimmune disease

When the immune system of body trigger against its own body cells and show the excessive action then the allergic condition developed [15]. Allergens are the substances which initiate the allergic response. IgE antibodies are more common in this condition. Histamine is also present in allergic condition which are released from the Mast cells. Anaphylaxis is a condition developed when these allergens cause an acute to severe reaction and that sometimes proves fatal condition. In this case, the immune system becomes hyperactive and cause the death of own host cells instead of killing foreign pathogens. Thymus parenchymal cells have the ability to recognition the body own cells and prevent them from killing central tolerance process that is immunologic tolerance to self-antigens. During such diseases, the demarcation between the cortex and the medulla deteriorated and the medullar epithelial cells are also dispersed [16]. A rare autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy is an inherited syndrome and is because of alterations in the specific gene [14]. Such gene permits the illustration of tissue related particular proteins present in the thymic medulla. This disease also affects multiple endocrine tissues. As T cell production take place in the thymus gland and if there is any defect in thymocyte development, it leads to profound decrease in the production of T cell, which may result into immunodeficiency disease. Abnormality to the thymic epithelial cells leads to the T cells dysfunctions, which may result in chronic inflammatory disease in the host [11, 12]. The tolerance is failed due to available antigens in the tissue is because of the autoimmune illnesses. If there is a defect in the production of both T cell and B cell, it results into severe combined immunodeficiency (SCID). When the combine deficiency of T lymphocytes and B lymphocytes occurs together, then the condition developed is known as SCID. This is a rare congenital disease, which is initiated by the non-functional hematopoietic progenitor cells that act as precursor of the B lymphocytes and T lymphocytes. When this condition develops, there is decrease in the lymphocytes production which results into the thymus atrophy [16]. There are also some other factors which are responsible for the causation of

this disease such as IL-7 deficiency, recombination activating gene deficiency and common gamma chain deficiency. Another autoimmune disease in which the antibodies blocks the acetylcholine receptors at neuromuscular junction. This autoimmune disease is known as myasthenia gravis. This illness is categorized as softness and fatigability of the muscle and is triggered by autoantibodies depending T cell counter to the neuromuscular junction. Its exact cause is unknown; however, it is assumed that changes in the thymus and the thymic epithelial cells is one of the main causes of its pathogenesis [14, 15]. Sometimes, this disease is associated with thymic hyperplasia. This disease is commonly cured by the surgical amputation of the thymus which is known as thymectomy. The conditions like thymic hyperplasia or malignancy are nearly 70% more common in the patients suffering with such autoimmune disease. Type-1 diabetes is also an autoimmune-based disease, which results from the obliteration of β cells in the islets of Langerhans. The pancreas infiltrating T lymphocytes cause the destruction of the insulin producing cells in the islets of Langerhans. The body, in this case, does not produce insulin. It is seemed to be more commonly present in adults. It has been observed that lack of immune tolerance to the β cells present in the pancreas is the initial cause of such diabetes development. The Human immunodeficiency virus (HIV virus) effect the developing lymphocytes and results into killing of these cells [18]. When the lymphocytes decrease in the body, then the T cell immunodeficiency syndrome occurs, which are acquired in nature. The HIV virus usually cause the killing the CD4 T cells and it also mainly effect the mature T lymphocytes which are present at the periphery. In this case, a rapid atrophy of the thymus takes place in the infected individual.

9.2 DiGeorge syndrome

This inherited ailment is because of the obliteration of a minor piece of chromosome-22, which is one of 23 pair of human chromosomes [17]. The syndrome affects the individual through various means like cleft palate, facial defects, delay development, learning problems, and promote infections. As far as the immunity is concerned, this syndrome leads to inherited shortcomings containing thymic atrophy and aplasia. Such affected persons may have intense deficiency of T cell lineage. In this disease, the thymic parenchymal cells are lost and the area is then replaced by the stromal CT.

9.3 Tumors

Thymomas is a scarce neoplasia (benign in nature) arise from the thymic epithelial cells. In the thymoma patients, there are chances for the occurrence of a disease known as thymoma-associated multiorgan autoimmunity (TAMA). In these patients, the donor does not act like a basis of pathogenic T cells instead, the individual particular thymus gland yields the infected T cells which is directed toward its own body cells [19]. If the thymoma indicates the malignancy of the thymus gland, then its product is the defective T cells which are unable to recognize their own body cells as self-antigens. So that is why we can hardly distinguish this disease from GVHD. These types of tumors, usually 10–15%, are presented in the patients who are already suffering from myasthenia gravis. The symptoms include strong cough which sometimes get confused with bronchitis because the laryngeal nerve is compressed by the tumor. All thymomas are cancerous, but they are varied from each other in different aspects like some develop slowly and some tumors grow with the rapid rate and infect the surrounding tissue [20]. The treatment of this condition is the surgical removal of the infected part or whole gland.

Thymic lymphomas are tumors which originate from the thymocytes of the thymus gland. These lymphomas or leukemia acts like the precursors of the origin of the thymocyte are often classified as T acute lymphoblastic leukemia/lymphoma. Before 1950, the radiation was used to cure the people who are suffering from the enlarged thymus gland particularly the children. The post-operative complication in the treated people includes an elevated incidence of thyroid cancer and leukemia. The rare malformation of thymus gland includes the cervical thymus cyst which is something confusing with the tumors. In the literature, there is no as such detail study of the thymic cyst prevalence. There is no such common lesion appeared which are present in this condition. In the childhood, there are more chances of the thymic cyst and the ectopic cervical thymus than the adults.

10. Means to modulate the functioning of the thymus gland

Thymic involution with age has negative impacts on the immune system. Proper performance of the thymus and integral immune system are required to protect against disorders. With the advancements of the modern sciences, a technique named as photobiomodulation is newly employed to slower the process of thymic involution. This delayed process improves immunity and may add in extension of the individual lifespan. Another new method which reduce the thymus atrophy and boost the thymus functioning is the sex-steroid ablation therapies [14]. Genetics has also an important role for determining the initial thymus size and rate of involution. Many hormonal medications, surgical procedures, and applications of antioxidants are testified as replacements for the reversal of aging in atrophy of the thymus. Males display a trend of lower grade thymopoiesis in comparison to females. There are several procedures that can improve the normal physiology of the thymus gland which ultimately leads to strengthen the immune system active for prolong time [20]. Continuous use of dietary supplements like rosehips, echinacea, olive leaf, and cruciferous vegetables are tested to be connected to establishment of the thymus health. These supplements are comprised of glucosinolates. This substance is famous for fighting contrary to the tumorous cells and other malformations in the tissues. Vegetables especially cruciferous vegetables like cauliflower, Bok Choy, broccoli, and cabbage are good source of nutrients that trigger antioxidants and anti-inflammatory responses. This can also assist thymus function. Proper timely intake of antioxidants and various vitamins like E and C in the diet is mostly necessary. These are needed for proper functioning of the thymus cells [21]. Zinc is also a very useful micronutrient required for the growth and growth of the vertebrate. The immune system is very sensitive to zinc deficiency and produces the multiple disturbances like atrophy of the thymus parenchyma and the increased chances for a disease to occur [22]. Many genes which regulate thymus gland activity are under the response of metalloenzymes in which zinc act as metal. So, dietary supplementation is very necessary for the proper functioning of the thymus gland otherwise, there may be a serious consequence related to the synthesis of the T lymphocytes. Exercise on daily basis is additional tool to ensure blood circulation throughout the body and the thymus gland. In this way increased blood flow will ensure that thymus waste products are removed promptly and do not cause damage to the thymus. Furthermore, through the circulation the key nutrients reach around the body more rapidly which allow quicker recovery to take place. Thymus gland stimulate the production of white blood cells that help against infection by thymosin hormone. This thymus glandular extract regulates many other immune functions. The extract called as thymomodulin, obtained from bovine species and act as immune boosting activities in immunodeficient individuals. Such extract act as a substitute and work against respiratory

infections and many other infections like asthma, food allergies and hay fever. Olive leaf extract has a significant effect on thymocyte apoptosis and cell cycle progression to protect the thymus gland from toxicity. Tapping sternum is a practice which may also stimulate thymus gland. But this practice is a bit laborious. Organic acid has a positive effect on the immune system. It has been reported that sodium butyrate improves the thymus histology and ultimately improves the immune system of a body [23]. Probiotics are called as the group of beneficial bacteria. Probiotics are generally defined as the friendly living micro-organisms, when taken orally in an appropriate dose, exhibit a beneficial effect on the host health. When the probiotics is taken orally, they go along side of the lumen of the gastrointestinal tract and interact with the mucosal immune system. Here, the whole bacteria or its cell wall mediate a network of signal production and activate the immune system. They produce different kinds of cytokines and chemokines and result into the activation of T lymphocytes. Another model of mechanism of action of probiotics is that they can suppress the growth of pathogenic bacteria and help in the balancing of microflora environment in the gastrointestinal tract. Probiotics protect the body against the pathogens by the induction of direct killing, nutritional competency of pathogens, and meanwhile by triggering the gut-associated immune repertoire. Thymus gland is known as the “Master gland of immunity” [2]. It regulates the immune system by producing different types of chemical known as cytokines that enhance the migration of T lymphocytes and meantime enhances the immunity [20]. The probiotic fermented milk (PFM) is a nutritional supplement which is used to improve the histology of the thymus gland mean to say it will cause a decrease in cellular apoptosis and enhance the percentage of CD4/CD8 cells. The PFM enhance the production of different kinds of cytokines in the thymus gland. This type of milk is usually used in case of protein-energy malnutrition; which result into malfunctioning of the immune system. This milk or bacterial-free supernatant helps to improve the immune system by activating thymus gland activity. Commonly used probiotics are specific strains of the lactic acid bacteria. The main genus includes in the probiotics are the *Bifidobacteria*, *Streptococci*, *Lactobacilli*, *Enterococcus*, *Pediococcus*, along with some yeast. Some probiotics like *L. paracasei* CNCM I-1518 and *L. casei* CRL 431 have a toll like receptors through which they make an attachment with the intestinal epithelial cells. Here, they mediate the immune stimulation by producing cytokines such as IL-6 and protein 1, which is chemoattractant in nature. Most of the probiotics are physically strengthening the intestinal barrier by producing the mucus layer, which is secreted from the goblet cells in the intestine. This viscous and impermeable mucus layers protect the intestinal barrier also stimulate the IgA and motivate the immunity. The probiotics also improve the health of animal by producing low molecular organic acids such as acetic acid and lactic acid. They also produce high molecular weight antimicrobial compound known as bacteriocins. These have strong inhibitory effect on the pathogenic gram-negative bacteria, i.e., *H. pylori* and the *Salmonella* species [24]. They inhibit the growth of pathogenic microbes and improve the health of animals. The lactobacilli containing probiotic has the ability to protect the children and adults from antibiotic-associated diarrhea and reduces its risk. *L. acidophilus* or *L. casei* are those probiotics can regulate the composition of microbial species present in the gut at balance level and suppress the growth of pathogenic bacteria. *L. acidophilus* or *L. casei* and lactic acid bacteria together act and result into suppressing the fecal coliform and other anaerobic bacteria. Some probiotics are also responsible for the shifting of microbes of gut to the beneficial bacteria, e.g., *Prevotella* and *Oscillibacter*. These bacteria are responsible for the production of anti-inflammatory metabolites. It can cause decrease the polarization of Th17 which favors the differentiation of anti-inflammatory Treg/Type 1 regulatory T (Tr1) cells in the gut. The *S. thermophilus* and *L. acidophilus*

probiotics have ability to increase the intestinal integrity by enhancing the gene expression in tight junction signaling. These probiotics decrease the adhesion entero-invasive *E. coli* in HT29 and Caco-2 cells by the maintenance (actin and ZO-1) or enhancement (actinin and occludin) of cytoskeletal and tight junctional protein phosphorylation. Antimicrobial peptides produced by probiotics are now considered as the future of the new class of therapeutics because it produces lesser resistance and have a specific antimicrobial activity to protect the host. Different kinds of antimicrobial peptides like lysozyme, secretory phospholipase A2, defensins, defensin-like peptides (elafin and SLPI), and cathelicidins are produce from the paneth cells. These are the characteristics epithelial cells of the small intestinal which is located at the bottom of the intestinal crypts. The probiotics *B. subtilis* was found in improvement of the thymus microarchitecture in broilers [25]. Prebiotics are those high fibrous non-digestible food particles that are used as a source of energy for the beneficial bacteria like bifidobacteria and lactobacteria and symbiotic is the combination of the probiotics and the prebiotics. It modulates the host immune system and usually effect the intestinal microflora and regulate the immune system directly and indirectly. When symbiotic are administered during the embryo it enhances the proliferation of the lymphocytes by causing decrease in the cortex/medulla ratio of the thymus gland. In a research, a number of prebiotics like inulin (Pre1), Bi2tos (Pre2), and also a symbiotic composed of inulin and *Lactococcus lactis* subsp. *lactis* IBB SL1 (Syn1), a symbiotic composed of Bi2tos and *L. lactis* subsp. *cremoris* IBB SC1 (Syn2), is administrated in the early chick embryonic life in order to check its effect on the lymphoid tissue activity. *B. longum* and a prebiotic (Synergy 1) when administered into the body, can enhance the release of defensins from epithelial cells and they have antimicrobial activity. The outcomes of the research come in the form of enhance lymphocytes proliferation. When the Bi2tos were administered with *L. lactis* subsp. *cremoris* (Syn2) they caused reduction of the thymic cortex to medullary ratio [26]. This indicates the more spreading of the medulla without the effect on the cortex representing the subsequent impacts on the thymus.

11. Conclusion

The thymus is a part of primary immune organs, having excellent example of connection between the cellular organization and function. Not like other well-organized organs, the microstructure of the thymus parenchyma has the very complex meshwork, where T cells differentiate, proliferate, and die. Disorganized thymic architecture of the elderly and disease thymus added cavitation and FCT proliferation and atrophy. Moreover, defects in the thymus caused to lesser the production of T cells and the interruption of self-tolerance. This may result in worsening the development of disease. Consequently, the thymus is declared as one of the most significant organs in maintaining immunity and safeguard the host against progression of age and development of ailments. Subsequently, this gland acts a crucial part in health and disease. The size, architecture, and function of this gland decreases with progression of age. There are some possible pathways to modify the thymus microarchitecture and function, in order to progress the physiology during autoimmune diseases, infections, and aging.

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