Chapter

Bronchus-Associated Lymphoid Tissue (BALT) Histology and Its Role in Various Pathologies

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Abstract

The lower respiratory tract is in direct communication with the external environment for gas exchange to occur. Therefore, it is constantly exposed to allergens, antigens, bacteria, viruses, and a wide variety of airborne foreign bodies. Bronchus-associated lymphoid tissue (BALT), which develops in response to these exposures and is one of the most prominent representatives of mucosa-associated lymphoid tissue (MALT), is important for generating rapid and specific bronchopulmonary adaptive immune responses. Therefore, this chapter focuses on the lymphoid architecture of BALT, which was first discovered in the bronchial wall of rabbits, its inducible form called inducible BALT (iBALT), its immunological response mechanisms, and its roles in certain pathologies including infectious and autoimmune diseases as well as in allergic and malignant conditions. In conclusion, it is hypothesized that BALT plays an important role in maintaining health and in the development of lower respiratory tract diseases; thanks to the pulmonary immune system in which it functions as a functional lymphoid tissue.

Keywords: Bronchus-associated lymphoid tissue, local immune response, histology, inducible bronchus-associated lymphoid tissue, lung diseases

1. Introduction

The respiratory system is anatomically divided into the following two parts: upper respiratory tract (organs outside the chest: nose, pharynx, and larynx) and lower respiratory tract (organs inside the chest: trachea, bronchi, bronchioles, alveolar ducts, and alveoli). This system that performs three basic functions, i.e., air transmission, air filtration, and gas exchange (respiration), is functionally divided into two zones. These are the conductive zones (from the nose to the bronchioles) that act as a pathway for the delivery of inhaled gases, and the respiratory zone (from the alveolar canal to the alveoli) where gas exchange occurs. The branching pattern of the conducting passages is known as the tracheobronchial tree as it resembles the branching of a tree [1].

The lungs, the main organ of the respiratory system, are divided into two sections depending on the functions of their structural parts. These are the tubes that conduct air (bronchi and bronchioles) and respiratory tissue (alveolar ducts, alveolar sacs, and alveoli). Ventilated by a secondary (lobar) bronchus, each lobe of the lung is divided into smaller pyramidal-shaped segments known as the bronchopulmonary segments and is ventilated by a tertiary (segmental) bronchus [2].

The bronchi of the lower respiratory tract are vital in terms of respiratory aspects because they are responsible for the transmission and filtration of air as well as for key immunological functions.

1.1 Bronchial structure

The bronchial wall is microscopically composed of the following five sections: mucosa, muscle, submucosa, cartilage, and peribronchial connective tissue (adventitia) (**Figure 1**) [3].

The epithelial and lamina propria layers constitute the bronchial mucosa layer, which has the characteristics of the respiratory mucosa. The initial part of the bronchi exhibits a similar structure to that of the trachea, which is a pathway responsible for the transmission of air taken from the external environment into the lungs. The structure of the bronchial wall changes histologically at the point where it enters the lungs and transforms into intrapulmonary bronchi. In the beginning, the bronchial mucosa comprises a layer of respiratory epithelium with the same cellular composition as the trachea. The height of the cells of this ciliated layer, also known as the pseudostratified columnar epithelium, decreases in proportion to the diameter of the bronchus.

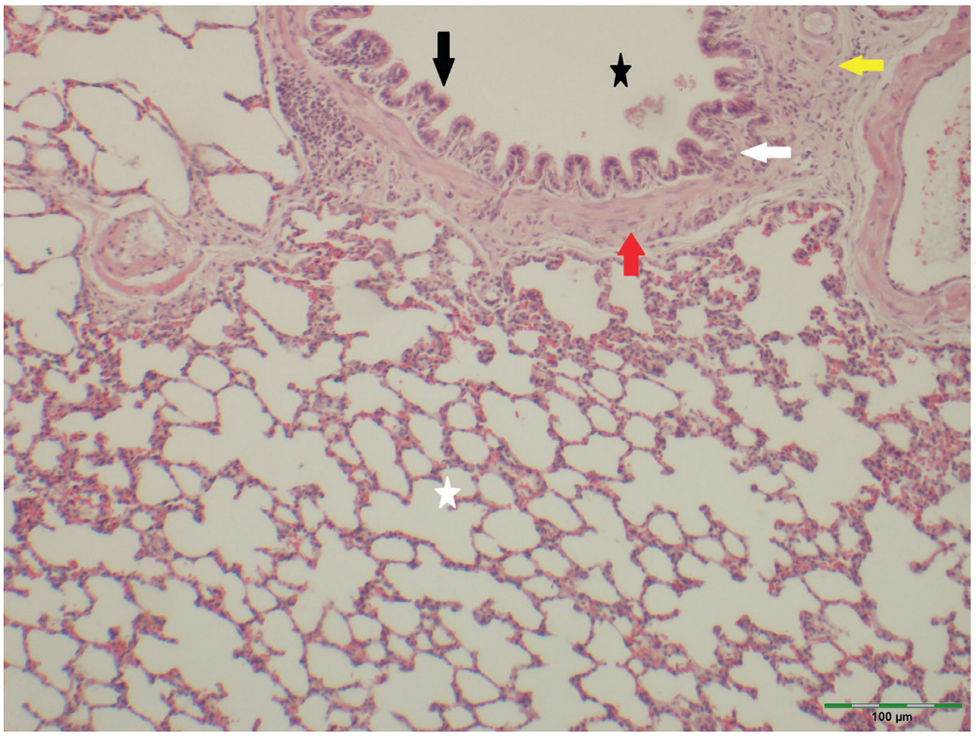

Figure 1.
Light microscopic view of the bronchial wall, rat lung (H-E). Black star: bronchial lumen, black arrow: respiratory epithelium layer, white arrow: lamina propria layer, red arrow: smooth muscle layer, yellow arrow: submucosa layer, white star: distinctive lung tissue (LT) showing the many empty spaces of pulmonary alveoli.

The prominent cell types in the epithelium are ciliated cells, goblet cells, basal cells, brush cells, and neuroendocrine cells. The epithelial layer is separated from other mucosal layers by a basement membrane [4].

The basement membrane is prominent in the primary bronchi; however, it rapidly decreases in thickness and disappears as a separate structure in the secondary bronchi. The lamina propria layer is similar to the trachea, but it decreases in proportion to the diameter of the bronchi. The lamina propria layer, which appears as a typical loose connective tissue with abundant elastic and collagen threads, is rich in cellular structures. In addition to the cell types such as plasma cells, mast cells, eosinophils, and fibroblasts, it comprises a large number of lymphocyte cells. The lymphocytes in this layer gather in the form of infiltrates at some places and lymph follicles at some [3].

The muscularis layer, which comprises multiple rows of circular smooth muscle cells, is a continuous layer of smooth muscles in the large bronchi. However, in the small bronchi, it is weakly and loosely organized because it may appear discontinuous due to its spiral route. This layer is responsible for determining the appropriate airway diameter for airflow regulation. In the large bronchi, the loose connective tissue submucosa layer is evident, whereas in the small bronchi, it is only observed as a narrow patch. In addition to the venous plexus and lymph follicles, bronchial glands known as GI. bronchioles are quite common in this layer. These glands, similar to salivary gland tissue, comprise a mixture of serous and mucinous cells and decrease in quantity as the diameter of the bronchi decreases (**Figure 2**) [3, 5].

The cartilage layer is observed as a whole in the trachea, whereas it is irregularly present at the beginning of the bronchi in the form of hyaline cartilage. As the diameter of the bronchus decreases, the fragmented cartilage layer becomes smaller and appears as elastic cartilage. On the other hand, the peribronchial connective tissue (adventitia) layer is dense that limits the bronchi from the alveoli and is rich in nerve and elastic fibers in addition to large blood and lymph vessels [3].

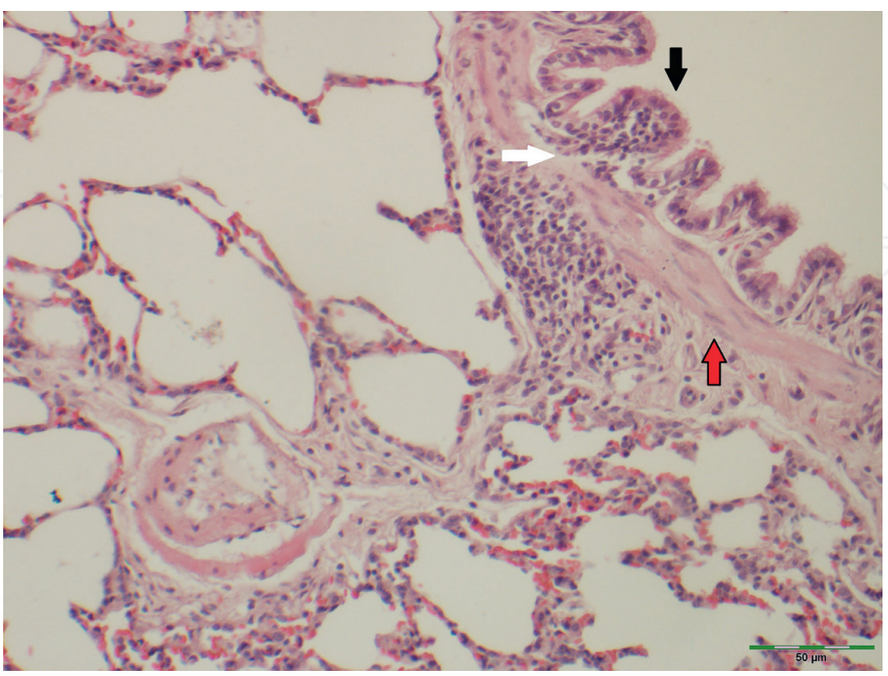

Figure 2.
A higher power light microscopic view of the bronchial wall, rat lung (H-E). Black arrow: respiratory epithelium layer, white arrow: lamina propria layer, red arrow: smooth muscle layer.

2. Bronchi immunology

The lower respiratory tract is constantly exposed to a wide variety of airborne foreign bodies because it is in direct communication with the external environment for gas exchange [6]. Both the trachea and bronchi function as filters against this exposure due to some of their structural features. The bronchial epithelium has a similar histological structure to the trachea and can capture foreign bodies through the smear of the mucus film secreted by the goblet cells to the kinocilium at the apical ends of the prismatic cells present in its structure. These bodies are captured and removed from the lungs by the movement of the kinocilium toward the larynx [7]. Mechanical filtering of inhaled air is thus ensured due to this primary defense mechanism.

The lower respiratory tract is constantly exposed to allergens, antigens, bacteria, and viruses during gas exchange. This is a very sensitive area for various types of pathogen invasions, such as influenza virus, measles virus, and *Mycobacterium tuberculosis* [8]. Producing rapid and specific adaptive immune responses against these factors are important for survival [6]. At the initial stage of an adaptive immune response, naive T cells migrate through the endothelial venules of blood vessels to secondary lymphoid tissues, where they are stimulated by antigen-bearing cells. This is critical for the development of appropriate adaptive immunity. This migration therefore leads to the generation of antigen-specific effector and memory T and B cells released from the secondary lymphoid tissue into the bloodstream. In the effector stage of the adaptive immune response, some memory T and B cells migrate from blood vessels to non-lymphoid tissues containing cognate antigens or pathogens [9, 10]. Bronchial lymphoid tissue and lymphatic nodes, two types of secondary lymphoid tissue found in the bronchial mucosa of the lower respiratory tract, are important in this regard [11, 12]. These secondary lymphoid tissues play a key role in the development of bronchopulmonary immune responses. Therefore, the bronchopulmonary adaptive immune system plays an important role in maintaining health as well as in the development of lower respiratory tract diseases [6].

The tracheobronchial tree, which is considered as an immunological organ, [13] is important for the defense mechanism of microorganisms reaching the lungs through inhaled air as well as for hypersensitive reactions that occur through respiration. The lymphoid tissue of the tracheobronchial system contains specialized diffuse, clustered, and solitary lymphatic nodules known as bronchus-associated lymphoid tissue [14, 15]. This secondary lymphoid tissue is a representative of the mucosal immune system in the bronchial wall, which is common in different parts of the body. It forms the immunoglobulins as a result of the immune defense reaction, thus forming a special protective mechanism of the lower respiratory system.

3. Mucosa-associated lymphoid tissue (MALT)

The immune system can recognize a wide range of unknown antigens and elicit an appropriate respond due to the lymphocytes that have a wide variety of antigen receptors [16]. This system has evolved into a system of secondary lymphoid organs such as the spleen, lymph nodes, Peyer's patches, and other MALT, in line with the defense targets [17]. Highly organized secondary lymphoid organs contain architectural domains that facilitate sequential cellular interactions between antigen-presenting cells and lymphocytes and efficiently promote the activation, selection, and differentiation of B and T cells [16]. Therefore, the immunological response becomes more effective.

MALT can function independently of the systemic immune system and therefore encompasses the mucosal immune system, which is a crucial part of immunopathology [18]. It plays an important role in immunological defense by eliciting immune responses against specific antigens encountered along the surfaces of all mucosal tissues [19]. Although MALT is anatomically divided into regions, these regions are functionally interconnected under the name of the common mucosal immune system. In this way, events such as antigen presentation and B-cell activation in a mucosal region can trigger the secretion of immunoglobulin A (IgA) in the mucosal regions of different organs [18, 20]. Due to MALT, which mainly functions to produce and secrete IgA along the mucosal surfaces in antigen-specific, T helper 2-dependent reactions, T helper 1 and cytotoxic T-cell-mediated reactions can occur. This may then result in immunotolerance [20, 21].

The best-known representatives of MALT, which contains approximately half of the lymphocytes of the immune system, [22] are gut-associated lymphoid tissue (GALT), nasal-associated lymphoid tissue (NALT), and BALT. However, structures such as conjunctival-associated lymphoid tissue (CALT), larynx-associated lymphoid tissue, and duct-associated lymphoid tissue (DALT) are other MALT representatives [20, 21].

MALT is divided into the two following functional parts: inducer sites and effector sites. Inducer sites include secondary lymphoid tissues, where the clonal expansion of B cells and IgA class transition occur in response to antigen-specific T-cell activation [19]. GALT, BALT, NALT, and CALT in mice, dogs [23], and baboons [24] and DALT in cynomolgus macaques [25] constitute these inducing sites. These sites are known as secondary immune tissues where antigen sampling occurs, and immune responses are initiated. Although there are many differences between inducing sites in various organs, they all contain the same functional segments as follows: lymphoid follicles, interfollicular zones, subepithelial dome zones, and follicle-associated epithelium or lymphoepithelium containing microfold (M) cells [19].

Effector sites distributed as diffuse lymphoid tissue throughout the lamina propria layer on all mucosal surfaces [26] are known as the transport sites of IgA along the mucosal epithelium. After activation and IgA class transition, T- and B cells migrate from inducing sites to these sites [19]. CD^{4+} and CD^{8+} T cells, IgA-, IgG- and IgM-plasma cells, B cells, antigen-presenting dendritic cells, and macrophages [19] constitute the cellular content of these effector regions where secreted IgA (S-IgA) is secreted along the mucosal epithelium [27]. Mast cells and eosinophils can occasionally be seen in the interfollicular area. Thus, all the cell types required to initiate an immune response are present here.

4. Bronchus-associated lymphoid tissue (BALT)

BALT, an important part of MALT, is classically used to refer to intrapulmonary lymphoid tissue in connection with the pulmonary vessels and adventitia of the bronchi [11, 28]. Macklin [29] named this lymphoid tissue in 1955 as 'sumps' or 'pulmonary tonsils' in which dust and organisms are retained. Subsequently, Bienenstock et al. [28, 30] identified these formations as subepithelial follicular lymphoid aggregates, primarily composed of lymphocytes, organized in the bronchial mucosa in contact with the surface epithelium, and coined the term BALT to describe them.

Although BALT, a secondary lymphoid tissue that plays an important role in the maintenance and regulation of lung mucosal immune homeostasis [8], was initially claimed to resemble Peyer's patches in the small intestine [11]; it was later revealed

that it was quite different from these formations [31]. Compared to GALT where in the founder Peyer's patches are located, it is accepted that BALT is not regularly present during fetal life due to embryonic preprogramming; however, it occurs with antigenic stimulation during the postnatal period [32, 33]. In other words, it is claimed that there is a relatively special lymphoid tissue in the development of BALT. However, studies have shown that BALT exhibits great differences between species [34, 35].

BALT, which was first identified in the bronchial wall of rabbits by Bienenstock et al. [28], is frequently detected in these animals and has the highest number of regions [28, 34]. In terms of the presence and distribution of BALT, rats and guinea pigs [34] follow rabbits, whereas germ-free pigs [28, 34], cats, dogs, and Syrian hamsters [34, 36] do not have this lymphoid tissue. BALT is frequently present in poultry, particularly hens [37]. In mice and humans, the situation with BALT is a little more contradictory [19]. Some scientists suggest that BALT is present in germ-free mice when antigenic stimulation is absent [12], whereas others report that it is not [38, 39]. Besides the differing viewpoints on the presence of BALT in mice, it is assumed that it is only observed infrequently after the neonatal period.

Further, it is claimed that BALT is not present in structurally healthy humans [31] because the features similar to BALT in mice are also found in humans [8]. BALT, in particular, is detectable if it is induced in adults; however, it is only observed in 40% healthy children and adolescents. Factors inducing the presence and distribution of BALT in these adults include infection, pathogen exposure, chronic pulmonary inflammation or autoimmune disease, etc. [32, 33, 40]. Moreover, it is suggested that the formation, size, and amount of BALT depend on the type and duration of exposure [41]. Therefore, it is concluded that BALT varies in different species as well as indifferent physiological states of the same species [8].

4.1 Inducible BALT (İBALT)

Most of the secondary lymphoid organs found in mice and humans develop embryonically in the absence of microbial stimulation or environmental antigens [42]. Furthermore, the structure and function of several secondary lymphoid organs, particularly those on the mucosal surfaces, are dramatically altered upon exposure to foreign antigens and commensal organisms [43]. Peyer's patches of MALT demonstrate a striking increase in size and complexity following the colonization of commensals [44, 45]. Similarly, in rodents, NALT is not completely developed until the postnatal period; however, microbial exposure accelerates this process [46]. On the other hand, the appendix tissue of rabbits has the characteristics of the primary and secondary lymphoid tissues in terms of being functionally dependent on microbial colonization [47]. However, some lymphoid tissues, known as tertiary lymphoid tissues, develop only after environmental exposure to microbes, pathogens, or inflammatory stimulations. Interestingly, although the lungs of mice and humans normally lack organized lymphoid tissue, tertiary lymphoid structures are frequently observed in lung tissue [38, 48].

BALT is recognized as an inducible tertiary or ectopic lymphoid tissue, unlike the related secondary lymphoid organs. BALT develops during the postnatal period and at anatomically non-lymphoid sites. In terms of disease states characterized by chronic inflammation, infection, or autoimmunity, BALT formation can be induced, and these areas are then known as iBALT [32, 38]. iBALT is a classic example of tertiary lymphoid tissue because it does not develop on a preprogrammed basis; its creation, size, and number in the lungs depend on the type and duration of antigenic

exposure [31, 49]. iBALT regions are best characterized in the lungs of rodents and humans. They are observed in the lungs of mammals and birds as well as in possibly all air-breathing vertebrates [41]. The emerging arguments confirm the role of infectious agents, such as isolated lymphoid follicles in the gut, indicating that iBALT may develop in response to microbial exposure [32]. In contrast, BALT is said to have been discovered in germ-free rats [28] and mice [50] as well.

Unlike the classical BALT structure, iBALT does not always have an overlying lymphoepithelium, is not associated with a continuous airway, and can be located adjacent to small pulmonary arteries in the lung parenchyma [32]. However, as both BALT and iBALT have the same function, both tissue types are called BALT [48].

4.2 Microscopic structure of BALT

Microscopically, BALT is defined as a densely packed cluster of lymphocytes with follicular structures enveloped in a network of reticular stromal cells beneath a specialized airway epithelium devoid of cilium. These structures are claimed to be located along the main bronchial airways embedded in the airway wall with extensive lymphocytic infiltration of the epithelial layer forming a classical dome epithelium (**Figures 3** and **4**) [11].

Further, it is stated that BALT is present in bronchial tree bifurcations to capture respiratory antigens. In species, BALT develops in response to various stimulations rather than being constitutively present in the lung, whereas iBALT does not always have such a defined structure or precise localization in the lung [51].

As a part of the integrated mucosal system including GALT, NALT, and other secondary lymphoid tissue representatives, BALT is known to contain cell types that are responsible for eliciting an appropriate immune response. BALT is mainly defined as an organized structure comprising T- and B-cell domains, dendritic cells (DCs), stromal cells, and high endothelial venules (HEVs) in the T-cell region [38, 52–55].

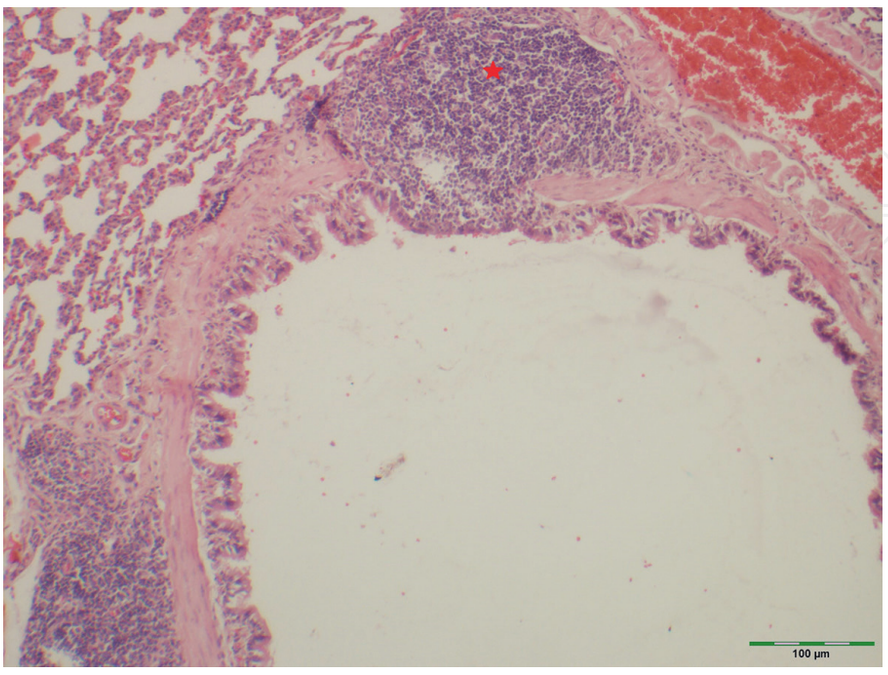

Figure 3.
Light microscopic view of the BALT structure, rat lung (H-E). Red star: BALT formation.

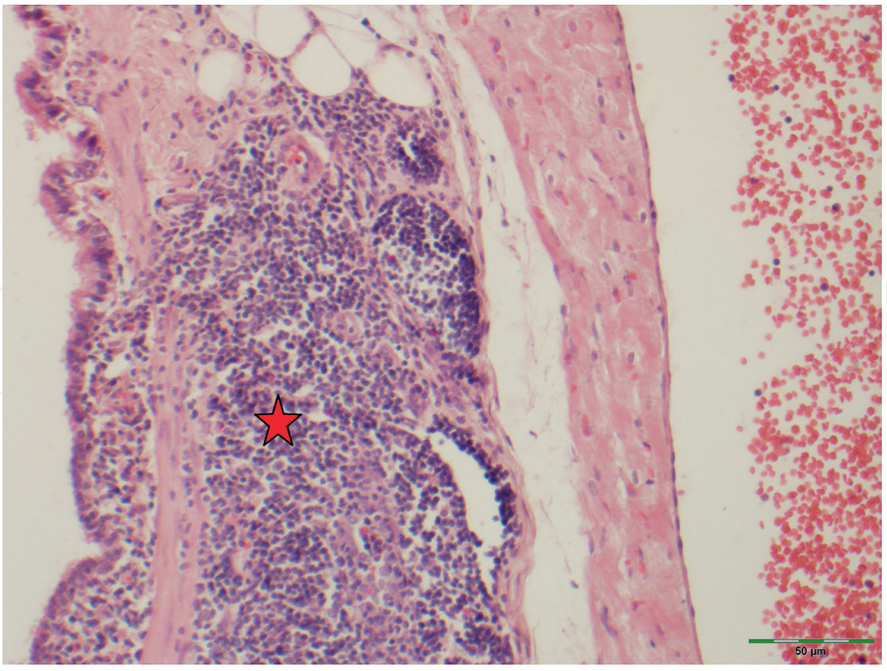

Figure 4.
A higher power light microscopic view of the BALT structure, rat lung (H-E). Red star: BALT formation.

Furthermore, it is stated that most of its cellular component consists of B cells expressing IgM^{lo} IgD^{hi}; however, depending on the nature of the microbe and/or antigen to which the cells respond, IgG-, IgA-, and even IgE-positive plasma cells may also be present [50, 56–58].

Moreover, in BALT, the most prominent structure is follicular-like lymphocyte accumulation, which is the common microscopic appearance of secondary lymphoid tissues, forming a classical germinal center (active site) [59, 60]. In this structure, surrounded by more mature, small lymphocytes, most of the germinal center comprises antigen-presenting macrophages [58, 61]. Lymphocytes leave the blood and migrate to BALT in the walls of HEVs, which are present at the periphery of the tissue. As there are no afferent lymphatics, these HEVs are thought to be the only entry site where lymphocytes migrate to BALT [59, 60]. In addition, the expression of chemokines in HEVs ensures accurate targeting of lymphocytes to lymphoid tissues [62].

However, in the direction of the bronchial epithelium, a dome-like protrusion similar to Peyer's patches toward the bronchial lumen is sometimes clearly observed [31]. The B-cell follicle, which is the most noticeable characteristic in classic BALT tissues with dome epithelium, is positioned below the epithelium [11]. CD^{4+} T cells are abundant in B-cell follicles, especially in reactive follicles with germinal centers [63], and CD^{8+} T cells are uncommon. Moreover, BALT is covered by a lymphoepithelium, which contains M cells that are similar to the M cells present in the dome epithelium of Peyer's patches in some species [31]. M cells are thought to transport antigens from the mucosal lumen to DCs that are in close contact with the dome epithelium [48]. Rabbits, the first and important representative of BALT, have fewer ciliated cells, few goblet cells, and many lymphocytes between epithelial and M cells. Although this basic structure appears to be valid for all species, there are some differences in details [31].

Another cell type that makes up the cellular component of BALT is follicular DCs (FDCs). These cells depend on the lymphotoxin signaling pathway to differentiate

into conventional lymphoid tissues and BALT [38]. Located at the center of B-cell follicles, these cells present antigen to B cells [64] and provide costimulatory signals that increase B-cell activation and proliferation in germinal centers [65, 66]. FDCs in mice are characterized by their ability to bind to antibodies against CD_{21}/CD_{35} [38], $FDCM_1$, or $FDCM_2$ [57] and to sequester their immune complexes [67]. In addition, FDCs are responsible for the organization of the follicle and expression of $CXCL_{13}$, which is responsible for the recruitment of B cells and some T cells in the B-cell area [68]. DCs located at the highest concentration in the T-cell areas of BALT are reportedly capable of preserving the BALT architecture as well as their antigen-presenting ability [48].

BALT is induced to produce IgA^+ cells that secrete polymeric IgA, mainly due to its role in immunity. When polymeric IgA is transported into the lumen, it induces the formation of S-IgA, which has considerable immunological importance [8]. Thus, when BALT is identified as part of the integrated mucosal immune system, the term should be restricted to structures tightly associated with an epithelium infiltrated by lymphocytes. In the integrated mucosal immune system, specific antigen uptake and antigen presentation by M cells occur and immune reactions are initiated, including IgA responses [31].

Immunohistological studies in humans show a preferential central localization of B cells mixed with some CD^{4+} lymphocytes and macrophages. CD^{4+} lymphocytes are also present in the area around the HEV, at the edge resembling a crown, and in the epithelium. In addition to the few proliferative cells positive for Ki67 observed in the follicles, many cells positive for the human leukocyte antigen-DR isotype, which is associated with various autoimmune conditions, disease susceptibility, and disease resistance, are evenly distributed in the follicle [69]. This basic structural distribution of lymphoid and non-lymphoid cells has also been noted in BALT in pathological conditions such as rheumatoid arthritis [70], hypersensitivity pneumonia [71], or diffuse panbronchiolitis [72]. Therefore, it is reasonable to conclude that BALT plays an important role in many respiratory system-related pathologies.

4.3 Role of BALT in various pathologies

BALT plays an important role in pulmonary immunity such as regulating microbial homeostasis [73], inducing immune tolerance [74], inhibiting inflammation [75], and supporting immune clearance [76]. Therefore, BALT frequently encounters many pathologies associated with infectious disease agents, allergens, environmental antigens, air-borne particles, autoimmune disease agents, and factors causing malignancy. As these pathological conditions have a broad spectrum, it is not possible to discuss all the roles of BALT; therefore, only a few have been addressed.

4.3.1 Role of BALT in resistance to infectious diseases

The respiratory tract is a typical entry site for viruses. This makes it difficult for the immune system to effectively eliminate viruses and virus-infected cells without causing much damage and inflammation, which jeopardizes the lung's structural and functional integrity. The balance between eliciting an immune response to effectively eliminate viruses and virus-infected cells and to cause less damage and inflammation is maintained by a complex network of innate and adaptive immune mechanisms as well as immunomodulatory and anti-inflammatory mechanisms. Accordingly, BALT could be one of the mechanisms that facilitates viral clearance by eliciting immune

responses and decreasing inflammatory responses [48]. BALT reportedly initiates pulmonary immune responses that are faster and more protective than those initiated at systemic sites. It has been proposed that once generated, BALT could play a key role in combating successive rounds of the same infection as well as assisting in establishing local immunity against unrelated viruses or pathogens [51]. For example, it has been suggested that *Lta*$^{-/-}$ mice without lymph nodes and Peyer's patches are more susceptible to the influenza virus and although they elicit immune responses, both B- and T-cell responses are delayed. Based on flow cytometric identification of germinal center B cells in the lung to question where immune responses might be initiated, it was concluded that both B- and T-cell responses are probably produced in the lungs [77]. BALT is suggested to be formed in the lungs of *Lta*$^{-/-}$ mice and locally initiates immune responses against influenza because the germinal center is present only in secondary lymphoid tissues. Another study reported that, in addition to germinal centers, plasma cells specific to influenza nucleoprotein were detected in BALT after influenza infection [58]. However, B-cell responses to influenza are accelerated in mice with pre-existing BALT, and morbidity and mortality rates are markedly reduced in response to a variety of viruses, including influenza, severe acute respiratory syndrome coronavirus, and mouse pneumovirus [78].

Mycobacterium tuberculosis (Mtb) infection is one of the serious health threats worldwide and is typically confined to the lungs. Although local immune mechanisms are primarily responsible for keeping Mtb infection under control, once the infection has settled in the lungs, immune mechanisms alone do not appear to be capable of eliminating these bacteria [79]. In humans, Mtb is localized to the granulomas comprising a central nucleus surrounded by macrophages, multinucleated giant cells, and lymphocytes [80]. The lymphocyte clusters surrounding these granulomas are B cells that form structures similar to BALT. These BALT areas associated with granuloma have B-cell follicles, and T-cell areas are present at the outer edge of the follicles [81]. Similar BALT domains, for example, have been discovered in murine models of Mtb infection, where B-cell clusters surrounding the granuloma were observed. Well-defined B-cell domains with FDCs are formed as early as day 42 after pulmonary infection and are protected from infection until at least day 90 [82]. Considering the link between B follicular structures surrounding the granuloma and Mtb uptake, another study showed that B-cell follicles formed around Mtb lesions in mice developed large germinal centers, and the B cells responded to the antigen [83]. Therefore, it is indicated that BALT initiates local pulmonary immune responses against Mtb infection via B cells.

4.3.2 Role of BALT in pulmonary responses to allergens and environmental antigens

Endotoxin, known as lipopolysaccharide (LPS), is a component of the gram-negative bacteria [84, 85] that is commonly present in the environment [86, 87]. The development or exacerbation of asthma [86, 87], bronchitis, and chronic obstructive pulmonary disease [88, 89] is linked to considerable LPS exposure. LPS, a classical T-cell-independent B-cell antigen, and mitogen are thought to bind to TLR_4 signaling pathway [84, 85], triggering B-cell activation, proliferation, and differentiation into antibody-secreting cells [90]. TLR_4 signaling activates macrophages and DCs, epithelial cells, and even fibroblasts, causing them to produce inflammatory cytokines and chemokines [91, 92]. Experimentally, pulmonary exposure of rats to endotoxin has been found to cause increases in pre-existing BALT and pulmonary plasma cells,

ultimately leading to the formation of germinal centers [93]. Sustained dosing of LPS prior to pulmonary inflammation in BALT-deficient mice appeared to result in BALT development in the major airways with an accumulation of B cells, T cells, and macrophages in the lungs, and even in BALT-deficient areas [94]. Thus, environmental exposures to LPS, often with additional antigenic or inflammatory components, cause BALT reactivity and pulmonary physiology alterations [95].

Considering the importance of pulmonary inflammation in asthma, a correlation between BALT development and asthma is likely. However, some believe that the presence of BALT is not always associated with asthma [96], but that the reactivity of BALT in patients with asthma is elevated [97]. Further, there is evidence that specific allergens, such as *Aspergillus fumigatus*, might cause pulmonary allergies that are similar to asthma. In allergic bronchopulmonary aspergillosis, large BALT regions characterized by diffuse and IgE-stained germinal centers have been found [98]. Thus, it is suggested that BALT can potentially contribute to allergic reactions by producing IgE locally in response to *A. fumigatus*.

Hypersensitivity pneumonia is defined as an inflammatory disease of the alveoli induced by hypersensitivity to inhaled organic antigens [99]. In contrast to asthma, which affects the airways, this condition affects the alveoli [48]. An occupational exposure often is the cause of hypersensitivity pneumonia; it can occur particularly when farmers are exposed to mold and fungi in barns [100]. Considering that hypersensitivity pneumonia results from chronic pulmonary exposure to the antigen, the emergence of well-developed BALT areas with vast germinal centers and FDC networks is not surprising for researchers [61].

4.3.3 Role of BALT in response to particles

The lungs are exposed to a wide range of particles, many of which are naturally inflammatory because they cannot be metabolized and persist in phagocytes or because their components bind to specific receptors that trigger an inflammatory response. Silicosis, for example, is a chronic diffuse parenchymal lung disease caused by prolonged exposure to inhaled crystalline silica particles. Pulmonary silica exposure reportedly results in nodules of mononuclear cell infiltration at the location of silica deposition, leading to pulmonary fibrosis [101]. It has been proposed that pulmonary exposure of rats to silica causes silica-loaded alveolar macrophages to migrate across the epithelium and accumulate in BALT [102]. This is analogous to the kinetic observation of virus-activated DCs in the airways migrating from the epithelium to BALT [40].

4.3.4 Role of BALT in autoimmune diseases

Rheumatoid arthritis (RA) and Sjögren's syndrome (SS) are autoimmune disorders characterized by the formation of ectopic lymphoid follicles in target tissues. Ectopic lymphoid follicles in the joints are common in patients with RA [103]; whereas ectopic follicles in the salivary and lacrimal glands are common in those with SS [104]. These follicles are hypothesized to contain separate B- and T-cell domains, germinal centers, FDCs, and HEVs, and they contribute toautoimmunity by generating high-affinity autoreactive B cells and sparing autoreactive effector T cells. BALT areas are observed in lung biopsies from a subset of patients with RA and SS who develop lung disease. It has been suggested to range from very small isolated lymphoid follicles to large, highly organized clusters of B-cell follicles [61].

4.3.5 Role of BALT in pulmonary malignancy

BALT formation is frequently linked to lung inflammation and exposure to a variety of inflammatory stimuli. Therefore, it is not surprising that experimental exposure to an inflammatory agent via the pulmonary route results in BALT hyperplasia in rats. However, it is possible that an inflammatory agent, which has been linked to tumorigenesis, could also cause pulmonary adenocarcinoma [105]. Therefore, inflammatory responses in the lung can promote BALT and neoplasia at the same time. Indeed, considering the links between chronic inflammation and cancer development [106], it seems probable that BALT formation precedes tumorigenesis in such cases [48].

Local immune responses to pulmonary pathogens and antigens are clearly associated with BALT formation; thus, it is predicted that BALT development adjacent to pulmonary malignancies would also be beneficial for antitumor immune responses. A study demonstrated tertiary lymphoid tissue neogenesis induced by lymphotoxin: antitumor antibody fusion protein with the accumulations of CD^{4+} and CD^{8+} T cells, B cells, and PNAd-expressing HEVs [107]. Thus, it was hypothesized that the immune response necessary for tumor eradication was produced locally in tertiary lymphoid tissues [108]. Therefore, it is concluded that local BALT induction surrounding pulmonary metastases may be beneficial in inducing antitumor immunity and tumor regression [48].

In addition, it is suggested that the development of a lymphoid environment surrounding tumors may trigger antitumor immunity or immunological tolerance due to some unknown factors. Further, some studies indicate that lymphoid-like stromal elements surrounding tumors can impair antitumor immunity and lead to tolerance [109]. Despite the discrepancies and gaps in the literature, the ability of BALT to be spontaneously developed as a clear response to the development of pulmonary tumors or metastasis of other tumors to the lung as well as to boost immunity against lung tumors is an intriguing and research-worthy topic.

5. Conclusions

BALT covers a large area in the lungs, from small irregular lymphocytes and DC clusters to B-cell follicles, germinal centers, FDCs, HEV lymphatics, well-developed dome epithelium, and highly organized lymphoid tissues. It has the potential to help researchers better understand the mechanisms underlying chronic lung diseases, particularly in mammals. The potential contributions of BALT at this point are the collection of antigens from the pulmonary airways, priming B- and T-cell responses, and aiding in the clearance of pulmonary diseases. BALT becomes a functional tissue due to the induction of T cells and the production of deep lymphoid tissue, which functions in priming immune responses in the lung, including IgA-secreting plasma cells. The development of effective vaccines, particularly in the prevention of viral infections, will be aided by lymphoid tissue production.

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