Journal of Medical Genetics and Clinical Biology
Homepage : https://journal.antispublisher.id/index.php/JMGCB
Email : admin@antispublisher.com

e-ISSN : 3032-1085
JMGCB, Vol. 2, No. 7, July 2025
Page 313-326

Tissue Organization of Mucosal Immune Responses: A Comparative Histological Analysis of the Respiratory and Intestinal Barriers

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DOI : https://doi.org/10.61796/jmgcb.v2i7.1347

Sections Info

Article history:
Submitted: May 31, 2025
Final Revised: June 15, 2025
Accepted: June 25, 2025
Published: July 02, 2025

Keywords:
Mucosal immune system
Lymphoid tissues
Epithelial-immune interaction
Immune microenvironments
Intestinal barrier

ABSTRACT

Objective: *Mucosal surfaces serve as critical defensive barriers that safeguard the organism from external environmental fluctuations and persistent pathogen threats. In response to these challenges, a specialized mucosal immune system has developed, which adapts through a process known as homing, allowing it to integrate with various tissues. This integrated immune system is responsible for producing, evaluating, and executing adaptive immune responses by establishing diverse immune microenvironments at mucosal locations. The present analysis centers on the similarities between the respiratory and intestinal mucosal systems, facilitating a comparative exploration of how a seemingly analogous system has evolved to fulfill the unique demands of different environments while preserving a robust foundational architecture.* ***Method:*** *Each mucosal microenvironment possesses distinctive features concerning its cellular composition, structural organization, and immune processes. To elucidate this well-characterized system, an examination of the invariant structural framework of these tissues will be conducted on both micro- and macro-scales, with an emphasis on the anatomy and cellular components of Peyer's patches (PP), bronchus-associated lymphoid tissue (BALT), conjunctiva-associated lymphoid tissue (CALT), tonsils, and isolated lymphoid tissues (ILT), along with smaller clusters found within the lungs.* ***Result:*** *Despite these specificities that may mitigate cross-competition among them, there is a proposition that the components of mucosa-associated lymphoid tissue (MALT) share evolutionary origins. A comparative analysis of the steady state microenvironments will delve into the complexities of immune engagement, the structural plasticity that facilitates intratissular memory, and the efficacy of effector responses that enable rapid pathogen clearance without incurring detrimental effects. Dendritic cells (DCs) residing in these environments play a pivotal role by capturing antigens utilizing various internalization receptorial setups and signal transduction pathways. The cross-presenting CD103+ DCs present in both mucosal systems influence the polarization of immune responses and the selection of immune strategies employed.* ***Novelty:*** *Finally, a succinct overview of the enhancing environments will be provided, addressing the proactive approaches adopted by pathogens and commensals, alongside the counterstrategies implemented by the immune system to address these threats. Special attention will be afforded to the collaborative roles of epithelial and immune cells in responding to viral infections and bacterial toxins.*

INTRODUCTION

The mucosal surfaces, which directly contact the external environment, are the sites where environmental antigens and pathogens enter the body. Despite having the same mucosal immunity structural site with distinct anatomical and architectural differences, various mucosal tissues display a characteristic mucosal immune system [1]. Over the past decades, experimental studies have offered substantial understanding of the mechanisms of mucosal immunity in animal models, particularly the gastrointestinal mucosal immune system, as the gut-associated lymphoid tissues (GALTs) were the first identified mucosal immune tissues. Recent advances in experimental approaches using newly developed genetically engineered mouse models have opened new avenues for

studying the respiratory mucosal immune system, including dissecting the cellular interactions in vivo [2]. The respiratory mucosal immune tissues consist of the nasal-associated lymphoid tissues (NALTs) and the small mucosa-associated lymphoid tissues (MALTs), such as the isolated lymphoid follicles (ILFs) in the nasal cavity and the gut-associated lymphoid tissues (GALT) [3]. These tissues develop in a defined time window and are characterized as lymphoid follicles containing B and T cell zones [4].

The mucosal surfaces are covered with a thin epithelial barrier, including goblet cells, enteroendocrine cells, Paneth cells, and M cells. The columnar epithelial cells form a dense layer sealed with intercellular junctions, including tight junctions and adherens junctions, which function as a barrier of the mucosa. Recent studies have revealed that the immune systems in different organs of the body, especially the mucosal immunity in the respiratory immune system and digestive immune system, exhibit various features and characteristics as per their anatomical and functional differences [5]. This review aims to discuss the differences between the respiratory mucosal immune system and gastrointestinal mucosal immune system, focusing on the cellular interactions constituting the respiratory and gastrointestinal mucosal immune systems. Understanding the mucosal immune system may aid in effectively preventing the spread of pathogens that invade the respiratory and digestive tracts and developing an effective mucosal vaccination strategy [6].

RESEARCH METHOD

Mucosal Immunology Overview

The human body faces constant threats from pathogens, making the immune system essential for balancing infection response without over-activation. Mucosal surfaces, which include the gastrointestinal, respiratory, and urogenital tracts, are the body's first line of immune defense as they directly interact with the external environment. These surfaces secrete mucus and antimicrobial substances to fend off various threats like pathogens and allergens. The mucosal immune system comprises mechanisms that provide specific immunity at these surfaces to combat external invasions. Different mucosal tissues have unique immune characteristics related to their structure and function [1].

The mucosal immune system includes both immune inductive and effector tissues. Mucosa-associated lymphoid tissues (MALTs) and draining lymph nodes are part of the inductive tissues, consisting of organized structures with T and B cell follicles, like the gut-associated lymphoid tissue (GALT) and nasopharynx-associated lymphoid tissue (NALT). The lamina propria (LP) within the mucosa stroma serves as the effector site containing T cells, plasma cells, macrophages, and dendritic cells. Immunoglobulins (Igs) play a vital role in this response, particularly secretory IgA (SIgA), which is essential for mucosal immunity. IgA is produced as a dimer by plasma cells in the LP and requires dimerization for secretion. SIgA is formed when dimeric IgA crosses epithelial cells and

is released on the mucosal side, binding to pathogens and allergens to prevent their entry and reduce allergic responses [7].

The Respiratory Mucosal Barrier

The respiratory tract is essential for airflow and acts as a primary defense in the mucosal immune system due to its extensive surface area. The respiratory mucosal barrier includes various tissues and cell types, differing from other mucosal tissues like the intestines. It is lined with epithelial cells that interact with immune cells organized into inductive and effector sites. The barrier comprises the upper tract (nasal cavity, sinuses, pharynx, larynx), lower tract (trachea, bronchi), and terminal bronchioles (MAMALT) [8]. The respiratory epithelium, sensitive to damage, contains specialized cells such as goblet, club, and multiciliated cells. Secretory IgA is transported through pIgR from the basolateral to apical membranes. Epithelial cells have microvilli and a layer of mucus, and submucosal glands secrete proteins and ions. The CTl system in the upper tract features a complex connective tissue organization beneath the epithelium. Paranasal sinuses connect closely to the nasal cavity through ostia openings, with the sinus lining continuous with that of the nasal cavity. The pharynx includes the nasopharynx and oropharynx, where the nasal cavity connects to the Eustachian tube. Waldeyer's ring comprises adenoid and tonsils, housing B cell-rich lymphoid follicles. The mucosa is structured into various sectors where immune cells are assembled or distributed. Type 1 supporting cells enhance ionocyte function by communicating NO signals to leukocytes to regulate immune responses in health [9].

Anatomy of the Respiratory System

The respiratory system generates both innate and adaptive immune responses through organized structures akin to the gut. The immune system's architecture in the respiratory system highlights the anatomy and histophysiology of immune response-related structures, including mucosa-associated lymphoid tissues (MALT) such as pharyngeal MALT, tracheobronchial MALT, pulmonary MALT (PALT), and the Grosses Glandules de Meibomius or "tubae auditivae." A detailed analysis emphasizes the similarities and contrasts with intestinal immune responses, enhancing the understanding of MALT broadly and respiratory MALT specifically [10] The airway mucosa interacts with various inhaled particles, from benign substances to significant airborne pathogens. Mucosal immunity in the airways is actively managed, utilizing both innate and adaptive responses to achieve homeostasis. Notably, the levels of secretory immunoglobulin A (SIgA) and secretory immunoglobulin M (SIgM) in the airway are low and high, respectively. Additionally, the airway MALT is anatomically distinct and contains immune effector cells, including γδ T cells, MALT, and innate lymphoid cells (ILCs), contributing to inflammatory response regulation [11]. The airways, extending from the nasal cavity to the alveolar sacs, encompass a complex anatomy, with nasal turbinates that warm and humidify incoming air while aiding respiratory rhythm. The respiratory tract, with multiple passageways from the mouth and nasal cavity converging at the larynx, leads to the trachea which bifurcates into the lungs. The conducting

airways, reaching terminal bronchioles, are lined with pseudostratified epithelium with mucus-secreting goblet cells, secretory club cells, and ciliated cells, transitioning in respiratory bronchioles to simple cuboidal epithelium and adjacent alveolar macrophages [12].

Immune Cells in the Respiratory Tract

The respiratory system contains various immune cells in distinct anatomical compartments, each with unique features. Pulmonary immune cells are classified into two categories: 1) parenchymal immune cells residing locally in lung tissue, and 2) migratory immune cells traveling from other organs or circulation to the alveolar airways. The lung parenchyma houses alveolar macrophages (AMs), interstitial macrophages (IMs), and dendritic cells (DCs). Most research has focused on interstitial and migratory macrophages; therefore, this text emphasizes AMs (Simukoko, 2021). After antigen uptake, CD11c+ DCs disperse throughout the airway interstitial fluid without a clear pattern, although PDL1+ DCs in conducting airways favor interactions with CD4+ T cells under normal conditions. Some lung DCs, like CD103+ DCs in bronchoalveolar lavage fluid, migrate to lymph nodes, critical for antigen presentation. The upper airway's pseudostratified epithelial layer consists of diverse cells involved in antigen uptake, mucociliary clearance, and maintaining respiratory homeostasis. Th-2 cytokines from Th-2 cells lead to goblet cell hyperplasia, increasing mucus production and causing allergic rhinitis. Viral infections can disrupt ciliary function, impairing mucociliary clearance. However, understanding of the upper respiratory tract's histological structure and cellular interactions remains limited, warranting further research using RNA-sequencing and intravital 2-photon microscopy [10].

Pathogen Recognition in Respiratory Mucosa

The respiratory mucosal surfaces of the lung and airways are constantly exposed to environmental antigens and pathogens, making viral infections a significant public health challenge. Therefore, controlling antiviral immune responses is essential. Understanding mucosal immune response organization sheds light on how the respiratory tracts achieve selective innate and adaptive immunity. Epithelial cells, type I IFN-secreting cells, and alveolar macrophages, triggering immune cascades influenced by the pathogen type, entry route, and antigen delivery method, recognize pathogens. Key factors in mucosal immunity include TLR3 expression in epithelial cells, crucial for strong antiviral responses, and RIG-I signaling that encourages Th1 immunity. The method of antigen delivery greatly impacts the immune response: intranasal delivery generates robust mucosal immunity while systemic routes, like intraperitoneal injection, fail to produce significant mucosal IgA or T cell responses, emphasizing the importance of delivery routes in immunological memory formation [13].

RESULTS AND DISCUSSION

The Intestinal Mucosal Barrier

The gastrointestinal tract (GIT) is lined with the largest mucosal surface area in the body, which functions as a main exposure route for various nutrients and commensal microorganisms, as well as digestive enzymes produced in the GIT lumen. However, a remarkable collection of immune components is also strategically organized in the GIT-associated lymphoid tissues, which provides the first-line defense against pathogens that invade through the mucosal surface. On the other hand, the commensal microorganisms that inhabit the GIT are indispensable for maintenance of host mucosal homeostasis [5]. Mucosal immune inductive sites of the innate immune system in the GIT are the gut-associated lymphoid tissues (GALT), which may include a large surface area of the protruding structures. The subepithelial dome (SED) contains B cell follicles that are not ripened into germinal centers (GCs) and is enriched with CD4+ T cells and an irregular cells at the follicle-associated epithelium (FAE) that can sample luminal antigens. In the lamina propria (LP) of the intestinal mucosa, effector T cells and IgA+ plasma cells, which are produced by the B1 cells in the SED, are localized [14]. In addition, γδ T cells are preferentially localized in the LP tissues compared with other mucosal tissues. Naive CD4+ T cells in the mesenteric lymph nodes (MLN) can be educated to differentiate into Th2 cells through exposure to type 2 induced by parasitic infection. Furthermore, to analyze cellular localization patterns of RNA, then known imaging mass spectrometry (IMS), and spatial transcriptomics based multiplex RNA detection assays can be applied to the intestinal mucosal barrier [15].

Anatomy of the Intestinal System

The gastrointestinal (GI) system and its organs vary significantly among animal species due to dietary adaptations, leading to diverse structures with specific functional characteristics while maintaining a common microscopic architecture. Key sections include the foregut (stomach), midgut (duodenum, jejunum, ileum), and hindgut (colon and rectum). Mammals exhibit advanced intestinal histology, especially complex stomachs [16]. The intestinal system typically has a single epithelial layer with enterocytes, goblet cells, enteroendocrine cells, and M cells. Oligodeoxynucleotide polymers (ODN) with phosphodiester bonds enhance immune cell survival, aiding inflammation. The connective tissue comprises fibroblasts, macrophages, lymphocytes, and mast cells. Studying vertebrate intestinal phylogenesis and ontogeny is vital in immunology and comparative anatomy [17].

Immune Cells in the Intestinal Tract

This barrier's high pathogen detection ability is due to the complex mucosal immune system it encounters. The GALT, formed through interactions between epithelial and immune cells, includes organized lymphoid tissues such as PP and MLN, as well as immune cells in the epithelium. M cells transport luminal antigens to immune systems at the PP and ILFs. A subpopulation of DCs associated with IELs presents antigens to mucosal T cells in the epithelium [18]. Additionally, B cells secreting

immunoglobulin A, generated through T-dependent or T-independent responses from ILFs and PPs, deliver sIgA throughout the intestine. However, compromised gastrointestinal barrier function can lead to excessive inflammation in conditions like inflammatory bowel disease and bowel cancer. Pathogens may be found near tight junctions between epithelial cells, and interactions between these cells and pathogens vary greatly. Aberrant mucosal immune responses cause inflammation and changes in the gut microbiome, while ongoing surveillance attempts to maintain equilibrium. In this changing environment, the adaptive mucosal immune system works to preserve sterility and homeostasis [19].

Pathogen Recognition in Intestinal Mucosa

Mucosal barriers composed of epithelial cells interact with intestinal content, regulating substance uptake to maintain immune homeostasis and protect against pathogens. Both respiratory and intestinal systems utilize mechanisms such as Toll-like receptors (TLRs), nucleotide-binding oligomerization domain-like receptors (NLRs), and peptidoglycan recognition proteins to detect pathogens. In the airways, TLRs mediate pathogen recognition, with TLR4 identifying Gram-negative bacteria through lipopolysaccharides and signaling through MyD88, TRIF, TRAF3, and NF-κB. TLRs activate keratinocytes and promote epithelial-immune interactions, inducing IL-25 and linking allergen recognition to asthma, while TLR2 is vital for IL-33 secretion [20]. NLRs enhance transcriptional capabilities of infected cells and inhibit cytosolic sensing by dephosphorylating TBK1. In the intestinal mucosa, TLRs recognize pathogens at the basolateral membrane, with Class A scavenger receptors aiding small RNA virus uptake. RIG-I-like receptors detect viral molecular patterns, optimizing pro-IL-1β mRNA translation, while C-type lectins identify various pathogens and stimulate NLR signaling, resulting in inflammatory responses and adaptive immunity. RIG-I-like cytosolic sensing recognizes viral RNA, triggering pro-inflammatory cytokine signaling and type I interferons [21].

Comparative Histology of Mucosal Barriers

The mucosal immune system comprises inductive and effector sites that manage immune responses. Mucosal inductive tissues, known as MALT, are organized lymphoid tissues located in the nasal cavity, respiratory tract, gut, and upper reproductive tract. MALT can appear as solitary or clustered isolated lymphoid tissues. These sites contain various cell types, including epithelial cells, antigen-presenting cells (APCs), and lymphocytes (B cells, T cells, mast cells) [22]. They generate mucosal immune responses by sampling luminal antigens through M cells and APCs, which convey antigens to lymph nodes, activating specific B and T cell subsets. MALT also secretes immunological molecules like antibodies and cytokines. Upon re-encountering pathogens, effector T and B cells move to mucosal tissue sites, recruiting innate immune cells, while effector T cells kill infected cells and regulate responses. Effector T cells migrate to the intestine, leading to the production of mucosal IgA, IgM, and serum IgG [7].

Cellular Composition

The mucosal immune systems are collections of immune cells located in mucosal sites, predominantly in the gastrointestinal and respiratory systems, as well as oral and urogenital regions. The gastrointestinal and respiratory tracts feature multiple layers, including an outer muscle layer for peristalsis and a mucosa-associated layer consisting of epithelium, lamina propria, and lymphatic tissues [3]. The epithelium acts as a barrier, with lamina propria cells scouting the surface. These systems include various immune and non-immune cells, with distinct distributions and arrangements forming unique tissue types. While some immune cells, like dendritic cells, appear in multiple sites, others are exclusive to specific locations. This variation alongside the presence of non-immune support cells may explain the differing responses observed in each tissue type [8].

Structural Differences

Mucosal tissues are vital organ systems for homeostasis and allostasis, characterized by differentiated epithelial barriers and connective tissues with diverse cell types in 3D structures. The respiratory and gastrointestinal tracts encounter distinct environments, leading to structural and cellular variations, yet both exhibit common principles of mucosal immunity through spatial actions of epithelial precursors along with effector and memory cell populations [3]. Effector outputs like IgA, IgM, and Th2 cytokines are crucial for nasal, bronchoalveolar, and gastrointestinal mucosa. Mucosal immunity is significantly influenced by biological factors such as microbes, food, air, and pathogens, which impact homeostasis and can lead to inflammation and allergies, harming health. Advances in cellular and molecular biology have enhanced insights into mucosal immune responses [23]. Despite similarities in effector responses, evolutionary and anatomical distinctions produce unique developmental designs and cell identities across mucosal surfaces. Studying immune responses in the lower respiratory and gastrointestinal tracts can illuminate unconventional mucosal surfaces and their immune roles [1].

Functional Implications

Mucosal barriers of TLOs serve as interfaces between mammals and their environment, exhibiting similar tissue organization but distinct structures. Nasal and ocular mucosal TLOs possess specialized features absent in intestinal TLOs, suggesting unique organ-specific functions. These differences imply diverse immunologic roles for mucosal immune responses across regions. The histological structure of TLOs, particularly the organization of germinal centers (GCs) and associated substructures, varies between species. Human and non-human primate TLOs contain more follicles and complex GC organization compared to mice and rats. This variation indicates a potential evolutionary shift in mucosal immune responses among species, possibly affecting immune targeting and lymphocyte movement dynamics [24].

Role of Microbiota in Mucosal Immunity

The gut contains trillions of microorganisms, including bacteria and viruses, relying on gut-associated lymphoid tissue (GALT) to sustain mucosal barriers and immune responses. This system helps identify invading pathogens and develop tolerance to harmless antigens. Chronic neglect of pathogens can lead to severe conditions like colon cancer and inflammatory bowel diseases. Skin microflora can impact immune responses; Th2 responses enhance IgE production but may overlook helminth infections, while Th1 microbiota can foster tumor growth and complicate immunotherapy [25]. Airway microflora also plays a role in gut health and respiratory infection vulnerability. Insights into T cell differentiation highlight the need for balance between Th1 and Th2 responses for effective mucosal immunity. The skin-associated lymphoid tissue (SALT) responds to injuries, which can cause inflammation and hair loss. The dermis contains immune cells and vessels, yet the maintenance and distribution of effector T cells from skin-draining lymph nodes are not well understood [26].

Microbiota Composition

Early colonization of the gastrointestinal tract (GIT) by microbiota significantly influences health. These microorganisms, coevolving with their hosts, include Bacteroidetes, Firmicutes, Actinobacteria, Proteobacteria, and Archaea, and are vital for physiological functions. The regulation of microbiota composition and its interactions with hosts is essential for gut homeostasis. Disruptions to this balance can lead to immune responses, resulting in dysbiosis or altered microbiota [27]. Dysbiosis is marked by an increase in harmful microbes and a decrease in beneficial ones, leading to excessive immune reactions and diseases affecting both the GIT, such as inflammatory bowel disease, and other organs, including the respiratory tract. This indicates that GIT dysbiosis can influence the respiratory system through microbial metabolites and immune cell interactions. Conversely, certain beneficial microbes manage immune functions and mitigate pathologies in the GIT and respiratory tract. Both systems share commonalities in immunoglobulin A (IgA) secretion, immune response tuning against pathogens, specialized dendritic cells for antigen sampling, and specific T cell differentiation, underscoring the interconnectedness of these mucosal surfaces [28].

Impact on Immune Responses

Mucosal immune responses to T-dependent and T-independent antigens activate the immune system in various mucosal tissues like the respiratory tract and intestine. In T-dependent responses, naïve CD4 T cells differentiate into Th cells through interactions with DCs and costimulatory factors, leading to Th1, Th2, or Th17 cells based on cytokines from DCs. Effector cell migration to sites is driven by chemokines [10]. T-independent responses involve polysaccharides activating marginal zone B (MZB) cells for Th-independent IgM responses, and polyclonal activators stimulating B1b and B2 cells for IgM production. However, these responses lack germinal center formation, limiting IgM's lifespan compared to T-dependent antibodies [29]. T-independent processes mainly yield IgM, while T-dependent responses generate IgA and IgG, post T-dependent

immunization. Mucosal immunization via nasal, oral, or vaginal routes elicits stronger systemic responses than parenteral routes, with nasal immunization enhancing antigen-specific IgG, IgA, and CTL responses more effectively than systemic or oral routes. Additionally, mucosal immunity responds to dietary substances due to high consumption levels [30].

Inflammatory Responses in Mucosal Tissues

The respiratory tract has pseudostratified columnar epithelial cells, including goblet and secretory cells. The mucociliary escalator traps pathogens, moving them to the pharynx for swallowing or expectoration. The lower tract comprises bronchi, bronchioles, and alveoli, where gas exchange occurs at the alveolar-capillary barrier formed by type I cells. Type II cells produce surfactant, and macrophages are present in the lumen [31]. The mucosal immune system is vital for pathogen defense, with upper airway components like nasal-associated lymphoid tissue (NALT), adenoids, and tonsils acting as mucosal-associated lymphoid tissues (MALTs). The nasal epithelium has columnar and basal cells, and mucus traps inhaled particles, processed by microbial flora in the nasopharynx. The olfactory epithelium detects pathogens, while MALT in the nasopharynx engages B and T cells for IgA production, enhancing immune responses and regulating nasal inflammation with repeated exposure [1].

Acute Inflammation

Inflammation can be both beneficial and harmful, causing organ failure and tissue damage. Smooth muscle contractions disrupt functions, while mucosal immune responses protect against diseases. Chronic inflammation impairs organ function through remodeling. Mucosal tissues have immunocytes for pathogen clearance, but excess inflammation leads to disease. Tissue microenvironments regulate macrophages, causing allergies. CD103+ DCs influence CD4+ Tr1 cell transformation into Th2 cells. Hyperplastic diseases involve abnormal tissue proliferation in mucosal tissues, with mutations altering architecture and linking faulty renewal to oncogenesis [32]

Chronic Inflammation

Mucosal surfaces, covered by epithelium, act as barriers against harmful microorganisms, but pathogens can still invade tissues, causing local inflammation. The host has systems involving epithelial and immune cells to control this inflammation, which can lead to chronic inflammatory diseases [33]. In the intestine and lungs, specialized columnar epithelial cells resist harmful bacteria and harbor goblet cells that secrete mucus and antimicrobial peptides. Mucus, primarily composed of heavily O-glycosylated mucins, forms a protective mesh, trapping pathogens, influencing microbiota composition while safeguarding epithelial cells, and facilitating fluid transport through cilia [1].

Mucosal Vaccination Strategies

Most viruses and bacterial pathogens infecting cattle, such as those causing bovine respiratory disease (BRD) and enteric infections, enter through the respiratory or gastrointestinal (GI) tracts, which are mucosal tissues. The mucosal immune system in

vertebrates, including cattle, defends against infections. Mucosa-associated lymphoid tissues (MALTs) are crucial for immune responses, divided into inductive and effector sites (Mach et al.2021). After antigen stimulation, B cells, T cells, and antigen-presenting cells (APCs) migrate to effector sites to perform immune functions [34]. Secretory IgA (sIgA), effector T cells, and macrophages help protect against infections. The respiratory tract is vital for defending against inhaled pathogens. MALTs include nasopharynx-associated lymphoid tissue (NALT) and bronchus-associated lymphoid tissue (BALT), with NALT essential for immunity against intranasal pathogens and the bronchi producing sIgA. Knowledge about the gastrointestinal tract's mucosal immune system remains limited. Pathogens like enterotoxigenic Escherichia coli and porcine epidemic diarrhea virus can cause high mortality in lactating piglets [35].

Pathological Conditions Affecting Mucosal Immunity

Mucosal surfaces play a central role in maintaining the human immune system's balance. The respiratory and gastrointestinal tracts exhibit diverse anatomical and functional features, reflecting evolutionary adaptations to specific environmental contexts. Immune system development depends, in part, on the maturation of the mucosal microenvironment, which is present at birth [5]. However, it is now understood that mucosal immunity is not fixed but can adapt to accommodate external stressors. Maladaptive immune responses can lead to the development of pathological conditions, such as aberrant protective immunity to allergens, commensal microorganisms, and autoantigens, which are commonly associated with a higher risk of asthma, allergic rhinitis, inflammatory bowel disease, and other allergic diseases [3]. On the other hand, chronic inflammation is also a risk factor for malignancies. This review focused on characterizing normal and aberrant immune responses of respiratory and gastrointestinal mucosal tissues associated to these physiological and pathological responses [1].

The upper respiratory tract represents a barrier to environmental threats and a pivotal site for modulating a sophisticated immune response. Dysregulated host immunity can trigger allergic inflammation in the upper and lower airways, leading to asthma symptoms. The nasal mucosa acts as the frontline barrier, directly sampling allergens into the epithelium and antigen-presenting cells (APCs). On the other hand, the lungs prevent the settlement of inhaled microorganisms in the lower airway and are the main site of protective immunity against respiratory viral infections and pneumonia [36].

Mucosal immune tissues of the GI tract produce a highly personalized immune response against various microorganisms (pathogenic and commensal). Across species, GI mucosa can produce an aberrant immune response to diet or microbiota aggravating the symptoms of IBD. The pathological study of tissues in mouse models of allergic inflammation and colitis has provided insights into adaptive immunity at mucosal tissues [37]. This review describes rigged mucosal architecture producing aberrant immune responses toward commensal, microbiota, allergens, or metabolites in both naturally occurring and animal model pathological conditions. By understanding the

pathological architecture, therapy targeting the origin of inflammation may be a more effective allergy treatment. On the other hand, a majority of traditional IBD treatment options are thought to target evolved regulatory immune mechanisms to switch the tissue immunity toward tolerance, exerting unwanted side effects, Celebi et al.

Allergic Responses

Allergic conditions like allergic rhinitis, asthma, and atopic dermatitis stem from abnormal mucosal immune responses. Mucosal vaccines show promise for managing these allergies, but understanding the immune mechanisms involved is still limited. mRNA-based vaccines are being researched for treating allergic diseases, which requires a better grasp of allergic mechanisms and the respiratory mucosa's structure [38]. Comparisons between respiratory and intestinal mucosa reveal that the respiratory mucosa serves as a key interface with the environment, containing varied microbiomes and allergens and possessing essential immune functions. Mucosa-associated lymphoid tissues (MALT), such as adenoids and bronchus-associated lymphoid tissues (BALT), exhibit germinal center (GC) reactions in nasopharyngeal MALT, though NALT and BALT are inactive in healthy individuals, with laryngeal MALT not fully reviewed [39]. The nasal cavity is mainly involved with respiratory viruses, yet its tissue organization and immune response to rhinoviruses (RV) are poorly understood. Differences between respiratory and intestinal mucosa include the early development of respiratory tissues in fetal growth and the absence of specialized immunogenic tissues, contrasted with the organized intestinal mucosa present at birth [40].

Autoimmune Diseases

Systemic autoimmunity involves antibodies against the body’s own substances, affecting the lungs and gut. In the lungs, autoantibodies may be present in blood without clear autoimmune symptoms but can indicate diseases in both animals and humans. Genetic predisposition and cigarette smoke disrupt alveolar macrophage-endothelial interactions, allowing autoantibodies to infiltrate tissues [41]. This situation triggers immune responses with high monocyte recruitment and low phagocytosis. In the gut, autoantibodies associated with ulcerative colitis interact with goblet cell mucins, impacting epithelial and immune functions. Cigarette smoke exacerbates RAAs and disrupts lung functions, highlighting the need to understand cell fate in research on disease manifestations in mucosal environments [42].

Infectious Diseases

The urinary tract relies on antimicrobial peptides, uromodulin, and mesenchymal stem cell exosomes for pathogen elimination due to the absence of innate lymphoid cells (ILCs). The urogenital tract employs both innate and adaptive immune responses to combat infections. Recent research highlights the gut-brain axis in multiple sclerosis [43]. CNS lymphatics are believed to drain interstitial fluid and immune cells, though meninges pathways remain unclear. Studies on respiratory and intestinal tracts emphasize mucosal immune system structures, while details on cellular compartment formation are less defined. The respiratory tract has fewer microfold cells (M cells) than

the intestine and a less organized immune structure, facing various airborne pathogens. Current vaccines prompt systemic immune responses but do not effectively stop pathogen entry, and a diverse respiratory microbiome could influence mucosal immune development [44].

CONCLUSION

Fundamental Finding : Gut-associated and other MALT tissues are classified into inductive and effector sites. Inductive sites are where naive lymphocytes encounter antigens and undergo differentiation. They include Peyer's patches, isolated lymphoid follicles, and gut-draining mesenteric lymph nodes (MLNs) in the intestine, as well as nasopharyngeal-associated lymphoid tissues (NALT), bronchus-associated lymphoid tissues (BALT), and palatine MLNs in the airborne pathogens. Effector sites are where effector lymphocytes migrate to serve their functions. They include surface tissues such as the intestine and lungs, as well as corresponding draining lymph nodes (dLNs). **Implication :** Tissue histology is established late embryonically or just after birth, resulting in two histological stages of GALT and BALT. Secretory IgA production is markedly increased before weaning and at roughly 5 weeks of age, when eating solid food, in parallel with histological changes of GALT tissues. They secrete IgM, IgG1, and IgG2 after first immunization. The tissue histology of respiratory tissues matures contemporaneously with IgA production. **Limitation :** Examination of parallel samples collected during early life can provide insights. **Future Research :** These studies are expected to provide basic information on MALT tissue organization, cellular composition, cell migration, and tissue-specific cellular interactions between a variety of cells and their molecules through comparison. Examination of qPCR and functional analyses will provide new insights into MALT functional development. MALT is categorized as gut-associated, mucosal, and other MALT.

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