The Respiratory Mucosal Barrier in Livestock and Poultry: Structure, Function, and Improvement Measures (Postprint)

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Abstract

The respiratory mucosal barrier constitutes a critical defensive barrier of the organism, primarily encompassing mechanical, chemical, microbial, and immune barriers that are organically integrated to collectively prevent invasion by harmful substances and safeguard respiratory health. Environmental factors such as dust, harmful gases, temperature, and humidity within livestock and poultry housing facilities can readily induce respiratory diseases, resulting in respiratory mucosal injury, exacerbating animal morbidity, and even precipitating pathological damage to visceral organs. This review primarily provides a theoretical foundation for further investigation of the respiratory mucosal barrier and the prevention and control of respiratory diseases in livestock and poultry by summarizing the structure and function of the respiratory mucosal barrier and strategies for its improvement.

Full Text

Structure and Functions of the Respiratory Mucosal Barrier in Livestock and Poultry and Strategies for Its Improvement

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Abstract: The respiratory mucosal barrier constitutes a critical defense system for the organism, comprising four primary components: the mechanical barrier, chemical barrier, microbial barrier, and immune barrier. These elements function in an integrated manner to prevent the invasion of harmful substances and

protect respiratory health. Environmental factors in livestock housing—including dust, harmful gases, temperature, and humidity—frequently trigger respiratory diseases, causing mucosal injury that exacerbates disease severity and may even induce pathological damage to internal organs. This review synthesizes current knowledge on the structure and function of the respiratory mucosal barrier and evaluates strategies for its enhancement in livestock and poultry, providing a theoretical foundation for further research on respiratory mucosal barriers and the prevention of respiratory diseases in domestic animals.

Keywords: livestock and poultry; respiratory tract; mucosal barrier; improvement measures

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The respiratory tract of livestock and poultry is continuously exposed to housing environments, subjecting it to constant challenges from temperature fluctuations, humidity variations, bacteria, viruses, dust particles, and various harmful gases. These hazardous substances can damage the respiratory mucosa or penetrate through intercellular spaces in airway epithelium, precipitating respiratory diseases. With the rapid development of intensive farming systems, respiratory diseases in livestock and poultry have become increasingly prevalent, leading to reduced production performance, compromised immune function, and in severe cases, direct mortality, thereby causing substantial economic losses to the livestock industry. Large-scale outbreaks of respiratory syndromes, infectious bronchitis, and influenza have heightened awareness of the critical importance of preventing and treating these conditions. As a major component of the mucosal defense system, the respiratory mucosal barrier directly interfaces with the external environment, isolating various harmful substances such as pathogenic microorganisms and dust from the internal milieu and serving as a vital protective shield for respiratory health.

The respiratory mucosal barrier efficiently clears airway pathogens, dust, and other foreign substances while resisting microbial infection and maintaining respiratory health. Therefore, a comprehensive understanding of barrier structure and function, along with the pathogenesis of respiratory diseases, is essential for developing therapeutic interventions, novel drugs, and advancing healthy animal production practices. Current literature has predominantly focused on intestinal mucosal barriers, with relatively limited research on respiratory mucosa, despite its crucial role as a primary defense against external hazards and a vital line of protection for organismal health. Furthermore, widespread prophylactic antibiotic use has led to the emergence of drug-resistant pathogens. This review aims to highlight the importance of respiratory mucosal barriers by summarizing their structural and functional characteristics and potential improvement strategies, thereby providing new research directions for enhancing animal health and vaccine development.

1 Overview of the Respiratory Mucosal Barrier

The mucosal system in animals primarily comprises respiratory and gastrointestinal mucosa, with the respiratory mucosa representing the second largest mucosal system and an effective barrier for maintaining respiratory health. The respiratory mucosal barrier consists of four integrated components—mechanical, chemical, microbial, and immune barriers—that protect the respiratory tract through distinct molecular regulatory mechanisms, signaling pathways, and biological functions. When various external pathogenic factors interact to disrupt barrier integrity, airway oxidative stress, inflammation, and infection ensue, leading to respiratory disease, diminished immune function, and potentially severe lung injury that seriously compromises animal health.

2.1 Mechanical Barrier

The mechanical barrier of the respiratory mucosa is formed by epithelial cells and intercellular tight junctions (TJ), which collectively prevent pathogenic microorganisms from penetrating deep tissues and constitute the structural foundation of the mucosal barrier. The respiratory epithelium [Figure 1: see original paper] comprises ciliated cells, goblet cells, basal cells, and submucosal secretory glands. Ciliated cells are the predominant cell type, bearing numerous cilia that beat rhythmically to clear bacteria, dust, and other harmful substances from the nasal cavity and trachea. When challenged by pathogens, viruses, or dust, ciliary function becomes impaired, reducing clearance capacity and prolonging retention time of harmful substances, ultimately triggering oxidative stress and inflammatory infection. Ciliated cells exhibit plasticity and can transdifferentiate into goblet cells, while goblet cells and Clara cells can differentiate into ciliated cells under certain conditions. Basal cells, anchored to the basement membrane via adhesion molecules, proliferate and differentiate to form new ciliated cells. Goblet cells and submucosal glands serve as primary secretory cells, protecting the mucosa through mucin secretion.

Intercellular junctions—including tight junctions, adherens junctions, and desmosomes—maintain epithelial structure and function through various junctional proteins and signaling molecules [Figure 2: see original paper]. Tight junctions represent the most critical junctional type, sealing intercellular spaces to prevent penetration of pathogens and foreign substances while maintaining internal homeostasis. Adherens junctions mediate cell-cell adhesion and intracellular signal transduction, whereas gap junctions facilitate material and information exchange essential for cell proliferation, differentiation, and organismal development. The tight junction complex comprises transmembrane proteins (occludin, claudins, junctional adhesion molecules [JAM]) and cytoplasmic proteins (zonula occludens [ZO] proteins ZO-1, ZO-2, ZO-3). These transmembrane proteins connect to the actin cytoskeleton via cytoplasmic proteins, forming integrated barrier structures that regulate permeability. Claudins constitute the primary structural framework, while occludin seals intercellular spaces, maintains polarity, regulates adhesion, and transduces cellular signals. ZO proteins link

transmembrane components to the cytoskeleton, transport signaling molecules, and maintain epithelial polarity, with ZO-1 and ZO-2 stabilizing the entire junctional system.

2.2 Chemical Barrier

The chemical barrier consists of a viscoelastic surface liquid layer covering the entire respiratory tract, comprising mucus and serous layers that maintain airway hydration and resist harmful factors. The mucus layer contains secretions from submucosal glands and epithelial cells, including defensins, lysozyme, antimicrobial peptides, and other components that disrupt bacterial cell walls. Mucus is primarily water (84–94%) with proteins, carbohydrates, and lipids, with mucins being the most important protein component. Mucins are classified as membrane-bound or secreted forms; membrane-bound mucins protect cells and facilitate bacterial adhesion, while secreted mucins lubricate and protect the barrier. Goblet cells and submucosal glands are the primary sources of respiratory mucins, with MUC5AC produced mainly by goblet cells and MUC5B by serous cells of submucosal glands. Under normal conditions, minimal mucus protects and lubricates the airway, but environmental stressors induce goblet cell hypertrophy and hyperplasia, upregulating MUC5AC expression and increasing mucus secretion that can obstruct airways. The serous layer provides an optimal environment for ciliary function, which is essential for mucociliary clearance.

2.3 Microbial Barrier

The respiratory mucosal surface harbors a stable community of microorganisms that interact with each other and the host to form a balanced microecological environment constituting the microbial barrier. Normal flora colonizing the upper respiratory tract aids in metabolism, nutrient absorption, and maintenance of mucosal immune homeostasis while resisting and clearing exogenous pathogens through competitive adhesion, antimicrobial secretion, and enhanced mucus production. In broilers, Shannon diversity and richness of laryngeal and tracheal microbiota increase with age, with Firmicutes, Actinobacteria, and Bacteroidetes predominating at the phylum level. Studies have identified Enterobacteriaceae as the primary respiratory microbiota in broilers, followed by unculturable microorganisms. At 21 days of age, the respiratory microbiota is dominated by Firmicutes, while at 42 days, both Firmicutes and Proteobacteria are predominant, with Lactobacillaceae, Bacillaceae, Enterococcaceae, Staphylococcaceae, Streptococcaceae, and Enterobacteriaceae being the dominant families. The unique structure of the respiratory tract makes it vulnerable to environmental perturbations, and dysbiosis can precipitate various respiratory diseases.

2.4 Immune Barrier

The respiratory mucosal immune system comprises mucosa-associated lymphoid tissue (MALT) and diffuse lymphoid tissue. MALT serves as the afferent lym-

phoid region where antigens are captured by epithelial cells and presented to T and B cells by antigen-presenting cells (APCs), initiating immune responses. Diffuse lymphoid tissue functions as the efferent region where plasma cells and sensitized lymphocytes migrate via homing mechanisms to exert effector functions. Respiratory MALT consists of bronchus-associated lymphoid tissue (BALT) and nose-associated lymphoid tissue (NALT). Research indicates that chicken respiratory MALT develops at 4 and 7 days of age, establishing the structural foundation for respiratory immunity. Prior to 35 days, cell-mediated immunity predominates, while humoral immunity becomes dominant thereafter. NALT is richly distributed in the nasal cavity, with chicken nasal glands forming at embryonic day 18 and NALT achieving full maturity by 21 days post-hatch.

Diffuse lymphoid tissue, located in the lamina propria, includes intraepithelial lymphocytes (IELs) and lamina propria lymphocytes (LPLs). IELs maintain epithelial integrity, express CD and β-integrins, secrete interferon (IFN), interleukin (IL)-2, and IL-5, and exhibit antigen-specific helper functions and natural killer (NK) cell activity. LPLs comprise diverse immune cells including B cells, T cells, NK cells, and macrophages. Upon antigen stimulation, B cells secrete secretory immunoglobulin A (sIgA) via secretory component mediation, while T cells secrete transforming growth factor (TGF), IL-4, IL-5, IL-6, and IL-10 to mediate immune functions.

sIgA plays a crucial role in respiratory mucosal defense. Studies in pigs demonstrate abundant antibody-secreting cells in the respiratory tract, with IgA-secreting cells most numerous in the trachea, followed by pharyngeal and soft palate tonsils, and fewest in the lungs. sIgA, composed of two IgA monomers, one J chain, and one secretory component, prevents microbial adhesion, neutralizes antigens, and lyses bacteria. Respiratory APCs, primarily dendritic cells (DCs) and macrophages, express major histocompatibility complex (MHC) class II molecules. DCs migrate to mucosal surfaces to capture antigens, transport them to lymphoid tissues, and effectively activate T cells to initiate, regulate, and maintain immune responses. Macrophages constitute over 90% of immune cells on airway surfaces. Microfold cells (M cells) rapidly transport unmodified antigens to APCs, while mast cells process and present antigens, phagocytose microorganisms, and modulate immune responses.

Airway mucus contains essential immune defense molecules including sIgA, antimicrobial peptides, defensins, lysozyme, lactoferrin, and protease inhibitors that disrupt bacterial cell walls, interfere with bacterial pathways, and compete for nutrients. Respiratory epithelial cells express pattern recognition receptors (PRRs), MHC molecules, costimulatory molecules, and adhesion molecules to recognize pathogen-associated molecular patterns and initiate innate immune responses. These cells also produce inflammatory mediators, cytokines, and reactive oxygen species that regulate inflammatory cell survival, chemotaxis, and activation. For example, epithelial cells activate nuclear factor- B (NF- B) via Toll-like receptors to secrete lysozyme and protease inhibitors that eliminate invading microorganisms.

3.1 Enhanced Management and Housing Environment Improvement

Housing contaminants including harmful gases, dust particles, and pathogens directly damage respiratory mucosa. Ammonia exposure at 25 mg/kg significantly upregulates MUC2 mRNA expression in broiler tracheal tissue, while concentrations of 50–75 mg/kg significantly downregulate both MUC2 and Claudin1 mRNA expression. Comprehensive management strategies include: (1) optimizing microclimate conditions by maintaining appropriate temperature (33–35°C for newly hatched chicks, decreasing 2–3°C weekly to 18–23°C) and humidity (60–70% initially, 50–60% later), with stocking density controlled at 30–33 kg body weight/m^2; (2) implementing proper ventilation protocols (minimum ventilation in winter, maximum in summer); (3) conducting weekly disinfection and prompt cleaning; (4) utilizing chemical and physical deodorants such as calcium phosphate and zeolite to reduce harmful gas concentrations; and (5) adopting all-in/all-out production systems with thorough cleaning and disinfection during vacant periods.

3.2 Feed Additive Supplementation

Recent studies demonstrate that feed additives including vitamins and probiotics promote mucosal development and repair, maintaining respiratory health. Dietary vitamin A preserves epithelial structure and function, blocking pathogen invasion while modulating respiratory mucosal immunity and mitigating lipopolysaccharide (LPS) and ammonia stress. Vitamin A deficiency induces squamous metaplasia and desquamation, compromising barrier integrity. Probiotic supplementation enhances production performance, immune function, and respiratory barrier integrity. Lactic acid bacteria inhibit *E. coli* colonization, modulate respiratory microbiota diversity, and improve respiratory immunity. Practical applications include daily spraying of *Bacillus subtilis* at 10^8 CFU/mL (1 mL/m^3) or compound *Bacillus* at 4$×10^{8}$ CFU/mL (2 mL/m^3). Additionally, herbal extracts such as honeysuckle and astragalus enhance cellular repair capacity and improve mucosal barrier function.

3.3 Rational Immunization and Medication

Strategic immunization and medication effectively enhance local immune function. Key measures include: (1) mucosal vaccination via eye drop, intranasal, or aerosol routes for diseases such as Newcastle disease and infectious bronchitis. The porcine respiratory tract represents an ideal site for mucosal immunization; intranasal administration of attenuated *Mycoplasma hyopneumoniae* significantly increases IgA and IgG-secreting cells, enhancing local humoral immunity. Mucosal vaccination effectively stimulates respiratory immune cells to produce immunoglobulins and cytokines that strengthen mucosal immunity. (2) Judicious antimicrobial selection based on regional susceptibility patterns to minimize disruption of normal respiratory microbiota and preserve immune competence.

The integrated network of respiratory mucosal components is vital for maintaining respiratory health. While methodological advances have facilitated mucosal barrier research, fundamental questions regarding microbial interactions and mucosal immune mechanisms remain to be elucidated. Enhanced investigation of respiratory mucosal barriers and their underlying mechanisms will provide novel approaches for disease prevention and treatment, representing a critical priority for healthy animal production development.

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