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REVIEW ARTICLE

Innovative perspectives on pulmonary immune responses: Pathogens versus protectors

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Abstract

The pulmonary immune system serves as a critical frontline in the host's defense against invading pathogens. Understanding the dynamic interplay between invading pathogens and the host's immune defenses is essential for the development of innovative therapeutic strategies. This review explores the complex mechanisms underlying pulmonary immune responses, with a focus on the balance between pathogen virulence and host immunity. Relevant publications – including peer-reviewed articles, clinical studies, and technological advancements published between 2020 and 2025 – were identified through searches of electronic databases such as Google Scholar, PubMed, Scopus, and Web of Science. The findings reveal that pathogens employ sophisticated strategies to evade immune detection, such as modulation of host cell signaling pathways and the secretion of virulence factors. Conversely, the host mounts protective immune responses characterized by rapid activation of innate immunity, cytokine-mediated signaling, and the development of adaptive immune memory. Notably, recent studies have reported several novel biomarkers associated with enhanced pathogen clearance and tissue repair, highlighting their potential as therapeutic targets. This review provides new insights into pulmonary immune responses, highlighting the delicate balance between pathogen evasion and host defense mechanisms. By identifying key immune regulators and pathogen-specific vulnerabilities, it highlights potential targets for innovative treatments to enhance pulmonary immunity. These findings underscore the importance of interdisciplinary approaches in advancing knowledge of respiratory infections and immune defense.

Keywords: Host defense; Immune regulation; Pathogen evasion; Respiratory infections; Pulmonary immunity; Therapeutic targets

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1. Introduction

The respiratory system serves as the host's crucial frontline against the external environment, constantly exposed to a myriad of pathogens, including bacteria, viruses, and fungi, as well as environmental pollutants and allergens. The lungs are particularly vulnerable to these challenges due to their large surface area and constant exposure to airborne particles.[1-3] To counter these threats, the pulmonary immune system has evolved to detect and neutralize harmful agents while minimizing collateral damage to delicate lung tissues. Despite ongoing exposure, the lungs are equipped with a highly advanced immune defense network that maintains homeostasis and protects against infection and injury.[4-6] However, many pathogens have developed sophisticated mechanisms to evade or manipulate host immune defenses, leading to persistent infections, chronic inflammation, and respiratory disease. This review explores recent advancements in understanding the pulmonary immune responses, focusing on the complex interplay between evading pathogens and host immune defenses, and how innovative research is reshaping approaches to respiratory health.

The balance between pathogen invasion and immune protection is delicate, and its disruption can lead to severe lung diseases – such as pneumonia, tuberculosis, chronic obstructive pulmonary disease (COPD), and asthma. While these conditions are often linked to microbiome alterations, environmental pollutants, and allergens, pathogens still play a significant role. The recent emergence of novel pathogens, such as SARS-CoV-2, has further highlighted the urgent need to deepen our understanding of pulmonary immunity and to develop innovative strategies that strengthen protective responses while minimizing harmful inflammation.

This review explores the dynamic interplay between invading pathogens and the host's pulmonary immune defenses, highlighting cutting-edge research into the molecular and cellular mechanisms underlying pulmonary immunity. It emphasizes the dual role of immune cells and mediators as both protectors and potential contributors to tissue damage. By examining emerging therapeutic approaches – including immunomodulation, microbiome engineering, and advanced vaccine technologies – this review offers a comprehensive overview of current trends and future directions. A deeper understanding of these immune responses may lead to more effective interventions for respiratory infections and chronic lung diseases, ultimately improving global health outcomes.

2. Methods

This review article employs a systematic approach to synthesize current literature on pulmonary immune responses, focusing on the dynamic interplay between pathogens and host defense mechanisms. It incorporates a comprehensive analysis of both experimental and clinical studies to provide a holistic understanding of pulmonary immune responses. By incorporating diverse study types, the review ensures a robust exploration of innovative perspectives in this field.

2.1. Inclusion criteria

Studies included in this review met the following criteria:

(i) Focused on pulmonary immunity, including pathogen–host interactions, immune evasion strategies, and protective immune responses
(ii) Published in peer-reviewed journals between 2020 and January 2025, ensuring relevance to current scientific knowledge
(iii) Were available as full-text articles in English
(iv) Employed *in vitro*, *in vivo*, or clinical models to investigate pulmonary immune responses.

2.2. Exclusion criteria

Studies were excluded if they:

(i) Did not clearly focus on pulmonary immunity or lacked relevance to pathogen–host interactions
(ii) Were published only as abstracts, conference proceedings, or in non-peer-reviewed articles
(iii) Contained redundant or overlapping data without providing novel insights
(iv) Focused exclusively on non-respiratory systems or addressed only non-immunological aspects of pulmonary diseases.

2.3. Search strategy

A systematic search was conducted across major databases – including Google scholar, PubMed, Scopus, and Web of Science – using a combination of relevant keywords, including "pulmonary immunity," "pathogen–host interactions," "immune evasion," "lung protection," and "innovative therapies." Boolean operators (e.g., AND, OR) were used to refine the search strategy. Additional articles were identified through manual screening of reference lists from relevant articles. Only articles published in English between 2020 and January 2025 were considered. The initial search yielded 540 articles. After applying the exclusion criteria, 519 articles were removed. Following relevance screening, quality assessment, and evaluation of their focus on innovative perspectives in pulmonary immune responses, 21 articles met the inclusion criteria (Figure 1 and Table 1).

2.4. Study selection

The initial search yielded a broad range of articles, which were first screened based on titles and abstracts. Subsequently, full-text articles were assessed for eligibility according to the predefined inclusion and exclusion criteria. One independent reviewer conducted the screening process, and any discrepancies were resolved through discussion or consultation with a second reviewer.

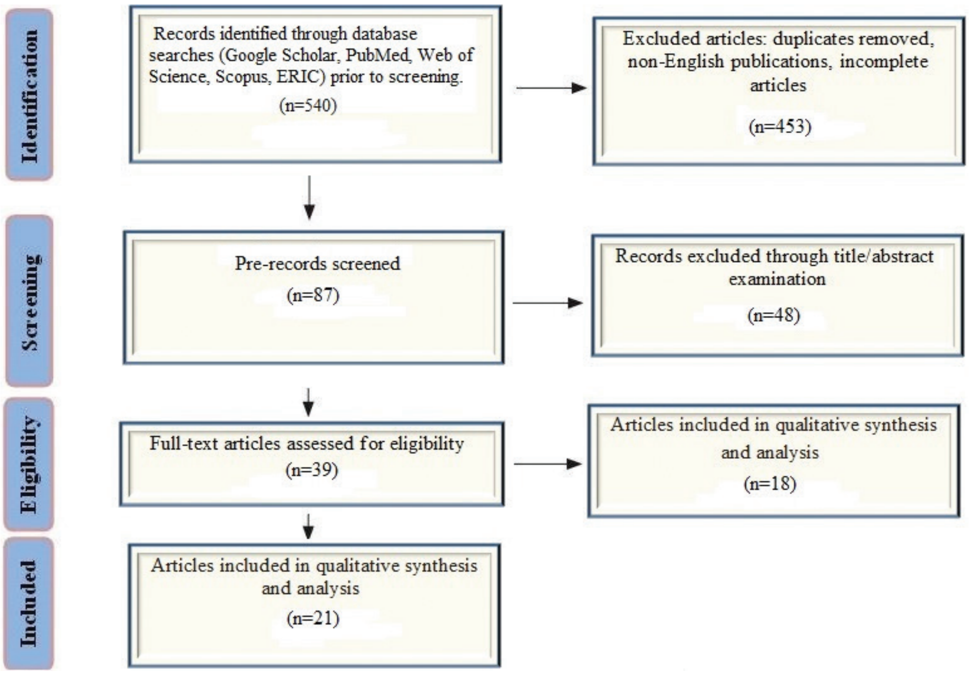

Figure 1. Flow chart of article screening
Abbreviation: ERIC: Education Resources Information Center.

Table 1. Key indicators used in the present review to evaluate core competencies in pulmonary immune responses

Results	Categories	Items	Example quotes	References
Enhanced understanding of immune mechanisms	Immune response pathways	Cytokine signaling, macrophage activation, and T-cell differentiation.	"Cytokine storms play a pivotal role in severe pulmonary infections."	43-45
Identification of novel biomarkers	Biomarker discovery	Protein markers, genetic signatures, and metabolic indicators.	"Elevated levels of protein X correlate with disease severity in patients."	46-48
Development of targeted therapies	Therapeutic innovations	Monoclonal antibodies, immunomodulators, and gene therapies.	"Monoclonal antibody Y shows promise in reducing viral load in preclinical models."	49-51
Role of microbiota in immunity	Microbiome-immune interactions	Gut–lung axis, microbial diversity, and probiotic interventions.	"The gut–lung axis modulates immune responses to respiratory pathogens."	52-54
Pathogens' immune evasion strategies	Pathogen adaptations	Antigenic variation, immune suppression, and biofilm formation.	"Pathogen X evades detection by altering surface proteins."	28,55,56
Protective host factors	Host defense mechanisms	Innate and adaptive immunity, and epithelial barrier function.	"Epithelial cells act as the first line of defense against invading pathogens."	57,58
Impact of environmental factors	Environmental influences	Air pollution, climate change, and occupational exposures.	"Exposure to particulate matter exacerbates pulmonary inflammation."	59,60
Advances in diagnostic tools	Diagnostic technologies	Artificial intelligence-based diagnostics, rapid testing, and imaging techniques.	"Artificial intelligence algorithms improve early detection of pulmonary infections."	61,62
Vaccine development progress	Vaccination strategies	mRNA vaccines, adjuvants, and mucosal vaccines.	"mRNA vaccines induce robust immune responses in the respiratory tract."	63,64
Cross-species immune comparisons	Comparative immunology	Animal models, evolutionary adaptations, and zoonotic infections.	"Comparative studies reveal conserved immune pathways across species."	65,66

2.5. Descriptive themes

The findings were organized into descriptive themes to highlight key insights:

(i) Pathogen strategies: Mechanisms employed by pathogens to evade or suppress pulmonary immune responses
(ii) Host defense mechanisms: Innate and adaptive immune responses that protect the lungs from infection
(iii) Innovative therapies: Emerging therapeutic approaches aimed at modulating pulmonary immune responses, including the use of immunomodulators and vaccines
(iv) Microbiome influence: The role of the lung microbiome in shaping immune responses.

3. Results

3.1. The pulmonary immune system

The pulmonary immune system is a complex and dynamic network that maintains a delicate balance between defending against pathogens and preventing excessive inflammation that could harm lung tissue. As a primary interface with the external environment, the lungs are constantly exposed to airborne pathogens, allergens, and environmental pollutants. This constant exposure necessitates a highly specialized and efficient immune response to provide protection while preserving respiratory function. This section explores the key components of the pulmonary immune system, emphasizing the interplay between pathogens and immune defense, and highlighting recent advances in research and emerging therapeutic strategies.

3.1.1. The pulmonary barrier: First line of defense

The respiratory epithelium, lined with ciliated cells and mucus-producing goblet cells, serves as the first physical and biochemical barrier against airborne pathogens. This epithelial layer is reinforced by antimicrobial peptides (AMPs), surfactant proteins, and secreted immunoglobulins that neutralize invaders before infection can be established. Recent studies have highlighted the crucial role of the epithelial barrier in shaping immune responses through the release of cytokines and chemokines, which recruit and activate immune cells.[7,8]

3.1.2. Innate immunity: Rapid and non-specific

The innate immune system in the lungs is characterized by its rapid response to invading pathogens. Alveolar macrophages – the most abundant immune cells in the airways – play a crucial role in phagocytosing pathogens and clearing apoptotic cells, thereby maintaining tissue homeostasis. In addition, dendritic cells act as immune sentinels, capturing antigens and migrating to lymph nodes to initiate adaptive immune responses. Neutrophils, while typically associated with acute inflammation, are also essential for combating bacterial and fungal infections. Recent research has highlighted the role of innate lymphoid cells (ILCs) in regulating mucosal immunity and tissue repair, offering new insights into their potential as therapeutic targets.[9]

3.1.3. Adaptive immunity: Precision and memory

The adaptive immune system provides a targeted and long-lasting defense against invading pathogens. T lymphocytes – including helper T cells such as Th1, Th2, and Th17, as well as regulatory T (Treg) cells – coordinate immune responses that are specifically tailored to distinct pathogens. On the other hand, B lymphocytes produce antigen-specific antibodies that neutralize pathogens and facilitate their clearance. Recent studies in single-cell sequencing have revealed significant heterogeneity within pulmonary T and B-cell populations, providing new insights into their roles in chronic lung diseases and vaccine-induced immunity.[10]

3.1.4. The microbiome: A double-edged sword

Once considered sterile, the lung microbiome is now recognized as a critical modulator of pulmonary immune responses. Commensal microbes contribute to immune homeostasis by competing with pathogens and modulating the immune system. However, dysbiosis – disruptions in the microbial community – has been linked to chronic inflammatory lung diseases such as asthma, COPD, and pulmonary fibrosis. Innovative therapeutic approaches – including probiotics and microbiome transplantation – are being explored to restore microbial balance and enhance pulmonary immunity.[11,12]

3.1.5. Immunopathology: When protection turns harmful

While the immune system is essential for protection, dysregulated responses can lead to immunopathology. Excessive inflammation – as observed in conditions such as acute respiratory distress syndrome or severe COVID-19 – can cause tissue damage and impair gas exchange. Conversely, inadequate immune responses, such as those in immunocompromised individuals, may lead to persistent infections. Understanding the mechanisms underlying these immune imbalances is crucial for developing targeted therapies that effectively modulate immune responses without compromising host defense.[13,14]

3.1.6. Innovative perspectives: Modulating the immune system

Recent advancements in immunology have laid the foundation for innovative strategies to enhance pulmonary immunity. These include:

(i) Immunotherapies: Monoclonal antibodies and immune checkpoint inhibitors are increasingly used to treat lung cancer and chronic respiratory infections
(ii) Vaccines: Advances in mRNA vaccine technology, highlighted by the success of COVID-19 vaccines, offer promising potential for preventing respiratory infections
(iii) Gene Editing: Clustered regularly interspaced short palindromic repeats (CRISPR)-based techniques are being explored to correct genetic defects in immune cells or enhance their protective functions within the lungs.
(iv) Nanotechnology: Engineered nanoparticles enable targeted delivery of drugs or vaccines directly to lung tissues, improving therapeutic efficacy while minimizing side effects.

a. *In vitro* models of lung epithelial cells

In vitro models of lung epithelial cells have become essential tools for investigating the early stages of pathogen invasion and the subsequent immune response. These models, typically derived from primary human bronchial or alveolar epithelial cells, closely replicate the structural and functional characteristics of the lung epithelium. By exposing these cells to pathogens – such as *Mycobacterium tuberculosis*,[15,16] influenza virus, or *Pseudomonas aeruginosa* – researchers can monitor real-time cellular responses, including the release of pro-inflammatory cytokines, disruption of the epithelial barrier, and activation of innate immune signaling pathways. In addition, these models facilitate high-throughput screening of potential therapeutics, offering a controlled platform to evaluate drug efficacy and toxicity before evaluation in more complex systems.

b. *In vivo* murine infection studies

While *in vitro* models of lung epithelial cells provide valuable insights into the early stages of pathogen invasion and the subsequent immune response, they cannot fully capture the complex interactions among immune cells, tissue architecture, and systemic responses present in a living organism. *In vivo* murine infection studies address this limitation by allowing researchers to examine pulmonary immune responses within the context of a whole organism. Mice – with their well-characterized immune systems and genetic manipulability – serve as ideal models for investigating host–pathogen interactions. For instance, studies using murine models have highlighted the role of alveolar macrophages in clearing bacterial infections and the contribution of T-cell subsets in controlling viral replication. In addition, transgenic and knockout mouse models have been pivotal in identifying key immune signaling pathways – such as the nucleotide oligomerization domain-like receptor protein 3 inflammasome and type I interferon (IFN) responses – that influence the outcomes of pulmonary infections.[17,18]

c. Advanced computational simulations

Alongside experimental approaches, advanced computational simulations have transformed the study of pulmonary immune responses. By integrating data from both *in vitro* and *in vivo* studies, these simulations can model complex immune networks and predict outcomes across various scenarios. For example, agent-based models simulate the interactions of individual immune cells and pathogens within the pulmonary microenvironment, providing valuable insights into spatial and temporal dynamics that are difficult to capture experimentally. Similarly, systems biology approaches utilize large-scale omics datasets to construct predictive models of immune signaling pathways, aiding the identification of potential therapeutic targets. Together, these computational tools not only enhance our understanding of pulmonary immunity but also facilitate the development of personalized treatment strategies

d. Innovative perspectives on pulmonary immune responses

The human respiratory system is a continuous battleground where pathogens and the immune system engage in a complex interplay of attack and defense. Recent advances in computational biology have transformed our understanding of these pulmonary immune responses, offering innovative insights into how the body defends itself against invading microorganisms. Advanced computational simulations have become powerful tools for dissecting and analyzing immune responses with unprecedented detail. By utilizing high-performance computing and machine learning algorithms, researchers can now model the dynamic interactions between pathogens and immune cells within the lung microenvironment. These simulations provide valuable insights into the spatial and temporal dynamics of immune responses, revealing how factors such as cytokine signaling, cellular migration, and pathogen evasion strategies influence infection outcomes. For instance, computational models have simulated the behavior of alveolar macrophages – the lung's first line of defense – and their interactions with bacterial or viral invaders. Such models can predict how variations in immune cell activity or pathogen virulence may shift the balance between effective clearance and chronic infection.[19,20]

In addition, advanced computational approaches facilitate the integration of multi-omics data – including genomics, transcriptomics, and proteomics – to construct comprehensive models of pulmonary immunity. These models help identify key molecular pathways and biomarkers that influence the progression of respiratory diseases such as influenza, tuberculosis, or COVID-19. For example, simulations have highlighted the critical role of IFN responses in controlling viral replication, as well as the detrimental effects of excessive inflammation in severe pneumonia cases. One of the most promising applications of these computational simulations is accelerating novel therapeutic development. By virtually screening thousands of drug candidates and their effects on immune–pathogen interactions, researchers can prioritize the most effective interventions for experimental validation. This approach not only reduces the time and cost of traditional drug discovery but also opens new avenues for personalized medicine, enabling treatments tailored to an individual's unique immune profile.

e. Microbiome influence

Once considered sterile, the human lung is now recognized as a dynamic ecosystem rich in microbial life. The pulmonary microbiome – a complex community of bacteria, viruses, fungi, and other microorganisms – plays a pivotal role in shaping immune responses within the respiratory system. This dynamic interplay between the lung microbiome and the immune system can influence whether these microorganisms act as harmful pathogens or beneficial protectors in the ongoing pulmonary immune response.

Recent research highlights the dual nature of the lung microbiome. A balanced and diverse microbial community contributes to immune homeostasis by training the immune system to distinguish between harmless invaders and genuine threats. For example, commensal bacteria can stimulate the production of anti-inflammatory cytokines and promote the development of Treg cells, which help suppress excessive immune responses and prevent chronic inflammation. This protective role is essential for maintaining lung health and resilience against infections.[21] Conversely, dysbiosis – an imbalance in the microbial community – can shift the balance toward pathogenicity. When harmful microbes dominate, they disrupt the epithelial barrier, trigger hyperactive immune responses, and exacerbate conditions such as asthma, COPD, and pulmonary fibrosis. Pathogens such as *P. aeruginosa* and *Streptococcus pneumoniae* exploit these imbalances, leading to persistent infections and chronic inflammation. Moreover, the interaction between the microbiome and viral infections, such as influenza or SARS-CoV-2, further complicates the immune response, as dysbiosis may impair the lung's ability to mount an effective antiviral defense.

Innovative perspectives are emerging to enhance the microbiome's protective potential while minimizing its pathogenic risks. Therapeutic strategies – such as probiotic therapies, targeted antimicrobial treatments, and microbiome transplantation – are being developed to restore microbial balance and enhance pulmonary immunity. Advances in metagenomic sequencing and machine learning are enabling researchers to explore the complex interactions between microbial communities and immune cells, creating opportunities for personalized interventions.[22] In pulmonary immune responses, the microbiome acts as both foe and ally. Understanding its influence is crucial for the development of novel therapeutic approaches that shift the balance toward protection, offering new hope to millions of individuals affected by respiratory diseases. As research on the lung microbiome progresses, one thing remains clear: these microscopic inhabitants hold the key to shaping the future of pulmonary medicine.

f. The balance between protection and pathology

The pulmonary immune system must maintain a delicate balance between eliminating pathogens and preventing excessive inflammation. Disruption of this balance can lead to chronic inflammatory diseases such as asthma, COPD, and pulmonary fibrosis. For instance, an overactive Th2 response characterizes allergic asthma, while excessive neutrophil activity is associated with tissue damage in COPD. However, this delicate balance between protection and pathology often acts as a double-edged sword. While robust immune responses are essential for eliminating harmful pathogens, excessive or dysregulated immunity can lead to tissue damage, chronic inflammation, and pathological conditions such as fibrosis or autoimmune disorders. Understanding this balance is critical for developing innovative therapeutic strategies that enhance protective immunity without shifting the balance toward pathology.

g. Protective immunity: The first line of defense

The lungs are constantly exposed to environmental pathogens, allergens, and pollutants, necessitating a rapid and efficient immune response. Innate immune systems – such as alveolar macrophages, dendritic cells, and epithelial barriers – play a pivotal role in detecting and neutralizing threats. These cells recognize pathogen-associated molecular patterns and damage-associated molecular patterns through pattern recognition receptors, initiating a cascade of pro-inflammatory signals. Neutrophils, natural killer cells, and AMPs further contribute to pathogen clearance, while adaptive immunity – mediated by T and B cells – provides long-lasting protection through memory responses.[23]

However, the effectiveness of these responses depends on precise regulation. For instance, alveolar macrophages exhibit a unique ability to switch between pro- and anti-inflammatory phenotypes, ensuring inflammation resolves once the threat is eliminated. Similarly, Treg cells play a crucial role in suppressing excessive immune activation and preventing collateral tissue damage.

4. Pathology: When protection goes awry

Despite these regulatory mechanisms, the pulmonary immune system is not infallible. Dysregulation can occur at multiple levels, leading to pathological outcomes. For example, excessive neutrophil recruitment and activation – while effective against bacteria – can release reactive oxygen species and proteases that damage lung tissue, contributing to conditions such as acute respiratory distress syndrome or COPD. Similarly, an overactive Th2 response to harmless allergens may trigger asthma, characterized by airway hyperresponsiveness and remodeling.[24] Chronic infections caused by pathogens such as *M. tuberculosis* or *P. aeruginosa* further disrupt this balance. These pathogens evade immune detection and persist in the lungs, driving sustained inflammation and tissue destruction. In some cases, the immune response itself becomes the primary driver of pathology, as seen in idiopathic pulmonary fibrosis, where aberrant wound healing and fibroblast activation lead to progressive scarring and loss of lung function.

5. Innovative perspectives: Restoring the delicate balance of pulmonary immune responses

Recent advances in immunology and biotechnology provide new insights into restoring the delicate balance between protection and pathology. Targeting specific immune pathways, such as cytokine signaling (e.g., interleukin [IL]-1β, IL-6, tumor necrosis factor α), shows promising potential in modulating excessive inflammation without compromising host defense. For instance, biologics like anti-IL-5 therapies have transformed the treatment of eosinophilic asthma by selectively suppressing harmful immune responses. Another innovative approach involves utilizing the power of the microbiome.

Once considered sterile, the lung microbiome is now recognized as a key player in immune regulation. Dysbiosis, or microbial imbalance, has been linked to chronic lung diseases, suggesting that restoring microbial diversity may help rebalance immune responses. Probiotics and prebiotics are being explored as potential therapies to achieve this balance. Furthermore, advances in gene editing technologies, such as CRISPR-Cas9, hold promising potential for correcting genetic defects that contribute to immune dysregulation. Similarly, personalized medicine approaches – guided by biomarkers and genetic profiling – aim to tailor therapies to individual patients, minimizing side effects and maximizing efficacy.

6. Pathogen evasion strategies: Evading the pulmonary immune defense

The respiratory system serves as the pathogen's primary target due to its constant exposure to the external environment. To successfully establish infection, pathogens have developed sophisticated strategies to evade the host's immune defenses. This review explores the complex mechanisms employed by pathogens to evade the pulmonary immune system, highlighting the ongoing battle between microbial invaders and host defenses.

6.1. Pathogen disguise and antigenic variation

Pathogens evade immune detection by altering their surface antigens, a strategy known as antigenic variation. For instance, influenza viruses frequently mutate their hemagglutinin and neuraminidase proteins, thereby enabling them to avoid recognition by pre-existing antibodies. Similarly, *M. tuberculosis* modifies its cell wall composition to avoid detection by pattern recognition receptors such as Toll-like receptors. This molecular mimicry allows pathogens to disguise themselves within the host environment, delaying immune recognition and response.

6.2. Inhibition of immune signaling

The pulmonary immune system is a complex network of cells, cytokines, and signaling pathways designed to protect the lungs against invading pathogens. However, many pathogens have developed sophisticated strategies to evade or inhibit immune signaling, shifting the balance in their favor. Conversely, excessive or dysregulated immune signaling can lead to chronic inflammation and tissue damage, highlighting the delicate interplay between protection and pathology. This section explores the mechanisms used by pathogens to inhibit immune signaling and the therapeutic potential of targeted immune modulation in pulmonary diseases.

6.2.1. Pathogen-mediated inhibition of immune signaling

Pathogens – including bacteria, viruses, and fungi – have developed diverse strategies to evade host immune defenses. For instance, *M. tuberculosis* inhibits macrophage activation and antigen presentation through multiple mechanisms. It secretes proteins – such as protein tyrosine phosphatase A and protein tyrosine phosphatase B – which dephosphorylate key host signaling molecules, including those in the mitogen-activated protein kinase and nuclear factor kappa B pathways, thereby suppressing pro-inflammatory cytokine production.

Similarly, respiratory viruses such as influenza A and SARS-CoV-2 encode proteins that disrupt IFN signaling.

The non-structural protein 1 of influenza A inhibits type I IFN production, while the open reading frame 6 protein of SARS-CoV-2 blocks the nuclear translocation of signal transducer and activator of transcription 1, a critical transcription factor for IFN-stimulated genes.[25-27] Fungal pathogens such as *Aspergillus fumigatus* also employ immune evasion strategies. They produce secondary metabolites like gliotoxin, which inhibits nuclear factor kappa B activation and induces apoptosis in immune cells. These pathogen-mediated disruptions of immune signaling not only facilitate microbial survival but also contribute to the progression of chronic pulmonary infections.[28]

6.2.2. Host-mediated inhibition of immune signaling: A protective mechanism?

While pathogen-mediated modulation of immune signaling is often detrimental, the host also downregulates immune responses to prevent excessive inflammation. Treg cells and anti-inflammatory cytokines – such as IL-10 and transforming growth factor β – play crucial roles in maintaining immune homeostasis. However, in chronic pulmonary diseases – such as asthma, COPD, and idiopathic pulmonary fibrosis – dysregulated immune signaling can lead to persistent inflammation and tissue remodeling. Therefore, targeted inhibition of specific immune signaling pathways has emerged as a promising therapeutic approach. For example, Janus kinase inhibitors have shown efficacy in suppressing cytokine storms in severe COVID-19 and autoimmune lung diseases.[29,30] Similarly, monoclonal antibodies targeting IL-4, IL-5, and IL-13 have transformed the treatment of eosinophilic asthma by selectively inhibiting Th2-mediated inflammation. However, the key challenge remains: suppressing harmful immune responses without compromising protective immunity.

a. Innovative therapeutic approaches

Recent advances in immunomodulatory therapies have introduced new strategies for targeting immune signaling in pulmonary diseases. Approaches such as small molecule inhibitors, biologics, and gene-editing technologies like CRISPR-Cas9 offer precise tools to modulate immune pathways. For instance, inhaled nanoparticles delivering small interfering RNA against pro-inflammatory cytokines can suppress inflammation locally, reducing the risk of systemic side effects. In addition, microbiome-based therapies are being explored to restore immune homeostasis in the lungs by modulating the gut–lung axis.[31]

b. The role of impaired mucociliary clearance (MCC) on the pulmonary microbiome and pathogen persistence

The MCC system is a critical defense mechanism in the respiratory tract, responsible for trapping and removing inhaled pathogens, pollutants, and cellular debris. When MCC is impaired – due to chronic respiratory diseases (e.g., COPD), cystic fibrosis, or primary ciliary dyskinesia – the lung microenvironment undergoes significant changes that disrupt the balance of the pulmonary microbiome and facilitate the persistence of harmful pathogens. Under normal conditions, MCC helps maintain a dynamic equilibrium in the lung microbiome by continuously eliminating microbes before they can colonize. However, impaired MCC leads to mucus accumulation, creating stagnant niches where bacteria can thrive.[32,33] Impaired MCC is not only unable to eliminate pathogens but also exacerbates inflammation. The resulting immune response further damages the airway epithelium, worsening MCC dysfunction in a vicious cycle. Prolonged inflammation alters the lung microenvironment, favoring pathogen adaptation and resistance.

6.3. Resistance to AMPs and phagocytosis

The pulmonary immune system relies heavily on AMPs and phagocytic cells such as macrophages and neutrophils to eliminate pathogens. However, pathogens such as *S. pneumoniae* and *Haemophilus influenzae* have developed resistance mechanisms to AMPs by modifying their cell membranes or secreting proteases that degrade these peptides. Furthermore, *Legionella pneumophila* and *M. tuberculosis* manipulate phagocytic cells, enabling them to survive and replicate within macrophages by inhibiting phagosome–lysosome fusion or resisting oxidative burst mechanisms.[31]

6.4. Biofilm formation

Biofilms are structured communities of microorganisms encased in a self-produced protective extracellular matrix. In the respiratory tract, pathogens such as *P. aeruginosa* and *S. aureus* form biofilms to shield themselves from immune cells and antibiotics. The biofilm matrix not only acts as a physical barrier but also modulates immune responses by trapping and neutralizing antimicrobial agents, thereby complicating treatment and contributing to chronic infections.[34,35] Biofilm formation begins with the attachment of planktonic (free-floating) microorganisms to the pulmonary epithelium or medical devices, such as endotracheal tubes. This attachment is facilitated by adhesins and other surface proteins that recognize host cell receptors or synthetic materials. Following attachment, the pathogens proliferate and secrete extracellular polymeric substances – including polysaccharides, proteins, and extracellular DNA – forming the biofilm matrix. This matrix not only provides structural integrity but also acts as a barrier against the host immune system – such as phagocytosis – and reduces the penetration of antibiotics.[36]

Within the biofilm, microorganisms undergo significant phenotypic changes, including altered metabolic activity and gene expression, which contribute to their increased resistance to antimicrobial agents.[37] This phenotypic shift is further exacerbated by the presence of persister cells – dormant subpopulations exhibiting high tolerance to antibiotics. In addition, biofilms facilitate horizontal gene transfer, promoting the spread of antibiotic resistance genes among microbial communities. The host immune system faces significant challenges in combating biofilm-associated infections. Neutrophils – the primary immune cells recruited to infection sites – often struggle to penetrate the biofilm matrix and instead release reactive oxygen species and proteolytic enzymes that can damage surrounding host tissues, contributing to chronic inflammation and tissue remodeling. Moreover, biofilms can modulate the host immune response by releasing virulence factors that disrupt signaling pathways and promote immune evasion.

6.5. Exploitation of immune checkpoints

Some pathogens exploit the host's immune regulatory mechanisms for their own advantage. For instance, *M. tuberculosis* upregulates immune checkpoint molecules such as programmed cell death protein 1 (PD-1) on T cells, thereby inducing T cell exhaustion and impairing adaptive immunity. By exploiting these regulatory pathways, pathogens effectively suppress immune responses, allowing them to persist in the host.

6.6. Exploitation of immune checkpoints in pulmonary immune responses

The immune checkpoint pathway, a critical regulator of immune homeostasis, plays both protective and detrimental roles in pulmonary immunity. While these checkpoints are essential for maintaining self-tolerance and preventing excessive immune activation, pathogens and tumors have developed sophisticated strategies to exploit them, enabling evasion of immune surveillance. In the lungs – a site of continuous exposure to environmental and microbial stimuli – this exploitation poses a major barrier to effective immunity and carries significant implications for respiratory health.[38] Immune checkpoints – such as PD-1/programmed death-ligand 1 (PD-L1) and cytotoxic T lymphocyte-associated protein 4 – are pivotal in modulating T-cell responses. Under normal conditions, these pathways ensure that immune reactions remain proportionate and targeted, thereby preventing collateral damage to delicate lung tissues. However, pathogens – including viruses such as influenza and SARS-CoV-2, as well as bacteria such as *M. tuberculosis* – have been shown to upregulate checkpoint molecules to suppress host immunity. For instance, during chronic viral infections or tuberculosis, the constant antigen exposure induces T-cell exhaustion, characterized by the upregulation of PD-1 on T cells and PD-L1 on infected cells or antigen-presenting cells. This interaction effectively dampens the immune response, allowing pathogens to establish chronic infections.[39]

The exploitation of immune checkpoints extends beyond infectious diseases. In lung cancer, tumor cells frequently manipulate these pathways to establish an immunosuppressive microenvironment. By expressing high levels of PD-L1, tumor cells engage PD-1 on cytotoxic T cells, leading to their functional exhaustion and impairing the anti-tumor immune response. This immune suppression has been a major focus of cancer immunotherapy, with checkpoint inhibitors such as anti-PD-1 and anti-cytotoxic T lymphocyte-associated protein 4 antibodies showing remarkable success in restoring T cell activity and improving patient outcomes. However, therapeutic targeting of immune checkpoints poses significant challenges. In the context of pulmonary infections, checkpoint inhibitors can trigger immune-mediated tissue damage, as seen in immune-related adverse events such as pneumonitis. Achieving a balance between restoring immune function and preventing immune hyperactivation remains a critical consideration in the development of immunotherapies for pulmonary diseases. Moreover, the interplay between immune checkpoints and the lung microbiome introduces additional complexity. Although it harbors a lower microbial density than the gut microbiome, the lung microbiome plays a crucial role in modulating local immune responses. Dysbiosis, or microbial imbalance, may influence checkpoint expression and function, potentially enhancing pathogen immune evasion or contributing to chronic inflammatory conditions such as asthma and COPD.

6.7. Modulation of host cell death pathways in pulmonary immune responses

Pathogens often manipulate host cell death pathways to evade recognition and elimination. For example, influenza viruses inhibit apoptosis in infected cells to prolong viral replication. Conversely, *M. tuberculosis* induces necrosis in macrophages, promoting bacterial dissemination while evading immune surveillance. By modulating cell death mechanisms, pathogens ensure their survival and propagation within the host.

The interplay between pathogens and the host's pulmonary immune system represents a complex and dynamic battle, in which modulation of host cell death pathways plays a pivotal role. Cell death mechanisms – including apoptosis, necrosis, pyroptosis, and necroptosis

– serve as critical defense strategies to eliminate infected cells and limit pathogen spread. However, pathogens have evolved sophisticated strategies to manipulate these pathways to their advantage, creating a delicate balance between protection and pathology.[40]

7. Innovative perspectives on pulmonary immune responses

Recent advances in immunology provide new insights into novel mechanisms and therapeutic targets in pulmonary immunity. ILCs – which mirror the functions of T-cell subsets but lack antigen-specific receptors – have emerged as key players. ILCs contribute to both protective and pathological immune responses in the lungs, offering new avenues for intervention.[41] In addition, the respiratory tract microbiome is now recognized as a critical modulator of pulmonary immunity. Commensal microbes influence immune cell development and function, while dysbiosis is linked to various respiratory diseases. Manipulating the microbiome through probiotics or targeted therapies holds promise for modulating immune responses.[42] Innovative technologies such as single-cell RNA sequencing and spatial transcriptomics provide unprecedented insights into the cellular and molecular dynamics of pulmonary immunity. These tools enable researchers to analyze the heterogeneity of immune cells within the lung and identify novel biomarkers and therapeutic targets.

8. Challenges and future directions

Despite these advancements, several challenges remain– – including the heterogeneity of pulmonary diseases, the complexity of host–pathogen interactions, and the risk of immune-mediated damage. Therefore, future research should focus on:

(i) Identifying biomarkers for early disease detection and personalized therapy
(ii) Developing universal vaccines against highly mutable viruses such as influenza
(iii) Exploring the role of the lung–brain axis and systemic immune responses in pulmonary health.

9. Conclusion

The battle between pathogens and the pulmonary immune system is a dynamic and evolving struggle. Advances in understanding immune mechanisms and pathogen strategies are paving the way for innovative therapies that enhance protection while minimizing harm. Through the application of cutting-edge technologies and interdisciplinary approaches, the balance may be shifted in favor of host defense, promoting healthier lungs and improved quality of life for patients worldwide.

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References

1. Dondi A, Carbone C, Manieri E, *et al*. Outdoor air pollution and childhood respiratory disease: The role of oxidative stress. *Int J Mol Sci*. 2023;24(5):4345.

   doi: 10.3390/ijms24054345

2. Besharati S. The expanding antibiotic resistance: The requirement of new therapeutic strategy for the development of new anti-infective. In: *Innate Immunity - New Perspectives and Therapeutic Opportunities*. London: IntechOpen; 2025. p. 49.

   doi: 10.5772/intechopen.1006935

3. Besharati S, Kalaleh AR. Personalized nursing and precision nursing: A concept of the future of the health model. *J Prev Diagn Treat Strategies Med*. 2024;3(4):227-234.

   doi: 10.4103/jpdtsm.jpdtsm_48_24

4. Block H, Zarbock A. A fragile balance: Does neutrophil extracellular trap formation drive pulmonary disease progression? *Cells*. 2021;10(8):1932.

   doi: 10.3390/cells10081932

5. Besharati S. The expanding antibiotic resistance: The requirement of new therapeutic strategy for the development

of new anti-infective. In: *Innate Immunity - New Perspectives and Therapeutic Opportunities*. London: IntechOpen; 2024.

doi: 10.5772/intechopen.1006935

6. Mojahed M, Besharati S, Farzanegan B, *et al*. Identification of operational errors in the stages of the hemovigilance program with the guidance of the Global Trigger Tool and comparing it with the reported errors. *Sci J Iran Blood Transfus Organ*. 2024;21(4):320-332.

7. Li R, Li J, Zhou X. Lung microbiome: New insights into the pathogenesis of respiratory diseases. *Signal Transduct Target Ther*. 2024;9(1):19.

doi: 10.1038/s41392-023-01722-y

8. Fröhlich E. Non-cellular layers of the respiratory tract: Protection against pathogens and target for drug delivery. *Pharmaceutics*. 2022;14(5):992.

doi: 10.3390/pharmaceutics14050992

9. Zhang H, He F, Li P, Hardwidge PR, Li N, Peng Y. The role of innate immunity in pulmonary infections. *BioMed Res Int*. 2021;2021(1):6646071.

doi: 10.1155/2021/6646071

10. Bizimana Rukundo T. Cross-reactivity in adaptive immunity: An overview. *Appl Sci (NIJBAS)*. 2024;5(3):39-43.

doi: 10.59298/NIJBAS/2024/5.3.394311

11. Whiteside SA, McGinniss JE, Collman RG. The lung microbiome: Progress and promise. *J Clin Investig*. 2021;131(15):e150473.

doi: 10.1172/JCI150473

12. Gillissen A, Paparoupa M. Inflammation and infections in asthma. *Clin Respir J*. 2015;9(3):257-269.

doi: 10.1111/crj.12135

13. Muyayalo KP, Gong GS, Kiyonga Aimeé K, Liao AH. Impaired immune response against SARS-CoV-2 infection is the major factor indirectly altering reproductive function in COVID-19 patients: A narrative review. *Hum Fertil* (*Camb*). 2023;26(4):778-796.

doi: 10.1080/14647273.2023.2262757

14. Saeid AB, De Rubis G, Williams KA, *et al*. Revolutionising lung health: Exploring the latest breakthroughs and future prospects of synbiotic nanostructures in lung diseases. *Chem Biol Interact*. 2024;395:111009.

doi: 10.1016/j.cbi.2024.111009

15. FarniaTP, Ghanavi J, Besharati S, Farnia P, Velayati AA. The pili at genomic level. *Pili in Mycobacterium Tuberculosis: Structure, Function, and Therapeutic Advances*. Netherlands: Elsevier; 2024. p. 161.

16. Fouladi MD, Besharati S, Farnia P, Khosravi A. A concise review of the effect of efflux pump on biofilm intensity in bacteria with a special view to mycobacterium. *J Prev Diagn Treat Strategies Med*. 2024;3(1):1-5.

doi: 10.4103/jpdtsm.jpdtsm_119_23

17. Mu P, Zhou S, Lv T, *et al*. Newly developed 3D *in vitro* models to study tumor-immune interaction. *J Exp Clin Cancer Res*. 2023;42(1):81.

doi: 10.1186/s13046-023-02653-w

18. Zong Y, Li H, Liao P, *et al*. Mitochondrial dysfunction: Mechanisms and advances in therapy. *Signal Transduct Target Ther*. 2024;9(1):124.

doi: 10.1038/s41392-024-01839-8

19. Zhou X, Wu Y, Zhu Z, *et al*. Mucosal immune response in biology, disease prevention and treatment. *Signal Transduct Target Ther*. 2025;10(1):7.

doi.org/10.1038/s41392-024-02043-4

20. Mochan E, Sego T. Mathematical modeling of the lethal synergism of coinfecting pathogens in respiratory viral infections: A review. *Microorganisms*. 2023;11(12):2974.

doi: 10.3390/microorganisms11122974

21. Qadri H, Shah AH, Almilaibary A, Mir MA. Microbiota, natural products, and human health: Exploring interactions for therapeutic insights. *Front Cell Infect Microbiol*. 2024;14:1371312.

doi: 10.1038/s41392-024-02043-4

22. Chiu CW, Tsai PJ, Lee CC, Ko WC, Hung YP. Application of microbiome management in therapy for Clostridioides difficile Infections: From fecal microbiota transplantation to probiotics to microbiota-preserving antimicrobial agents. *Pathogens*. 2021;10(6):649.

23. Land WG. The DAMP-driven host immune defense program against pathogens. In: *Damage-Associated Molecular Patterns in Human Diseases: Antigen-Related Disorders*. Vol. 3. Germany: Springer; 2023. p. 203-284.

doi: 10.1007/978-3-031-21776-0_4

24. Meng X, Layhadi JA, Keane ST, Cartwright NJ, Durham SR, Shamji MH. Immunological mechanisms of tolerance: Central, peripheral and the role of T and B cells. *Asia Pac Allergy*. 2023;13(4):175-186.

doi: 10.5415/apallergy.0000000000000128

25. Besharati S, Aghajani J, Farnia P, *et al*. Association between the Vitamin D Receptor Gene (FokI, BsmI, ApaI, and TaqI) polymorphism in health-care workers and susceptibility to COVID-19. *Biomed Biotechnol Res J (BBRJ)*. 2023;7(3):404-410.

doi: 10.4103/bbrj.bbrj_133_23

26. Farnia P, Besharati S, Farina P, *et al*. The role of efflux pumps transporter in multi-drug resistant tuberculosis: Mycobacterial memberane protein (MmpL5). *Int J Mycobacteriol*. 2024;13(1):7-14.

doi: 10.4103/ijmy.ijmy_37_24

27. Farnia P, Farnia P, Ghanavi J, Ayoubi S, Besharati S, Velayati AA. Comparison of proline-glutamate-proline-glutamate-polymorphic GC-rich sequences family protein Wag22 (Rv1759c), PE_PGRS31 (Rv1768), PE_PGRS32 (Rv1803), and *PE_PGRS33* gene (Rv1818c) in exponential state and under *in vitro* model of latency in same clinical isolates of *Mycobacterium tuberculosis*: Frameshift mutation in extensively drug-resistant and totally drug-resistant *Tuberculosis bacilli*. *Biomed Biotechnol Res J (BBRJ)*. 2023;7(4):621-632.

doi: 10.4103/bbrj.bbrj_271_23

28. Wang Y, Pruitt RN, Nürnberger T, Wang Y. Evasion of plant immunity by microbial pathogens. *Nat Rev Microbiol*. 2022;20(8):449-464.

doi: 10.1038/s41579-022-00710-3

29. Tanaka Y, Luo Y, O'Shea JJ, Nakayamada S. Janus kinase-targeting therapies in rheumatology: A mechanisms-based approach. *Nat Rev Rheumatol*. 2022;18(3):133-145.

doi: 10.1038/s41584-021-00726-8

30. Varahram M, Besharati S, Farnia P, *et al*. Correlation of single-nucleotide polymorphism at interferon-gamma R1 (at position- 56) in positive purified protein derivative health workers with COVID-19 infection. *Int J Mycobacteriol*. 2022;11(3):318-322.

doi: 10.4103/ijmy.ijmy_133_22

31. Lei L, Pan W, Shou X, *et al*. Nanomaterials-assisted gene editing and synthetic biology for optimizing the treatment of pulmonary diseases. *J Nanobiotechnol*. 2024;22(1):343.

doi: 10.1186/s12951-024-02627-w

32. Adivitiya, Kaushik MS, Chakraborty S, Veleri S, Kateriya S. Mucociliary respiratory epithelium integrity in molecular defense and susceptibility to pulmonary viral infections. *Biology* (*Basel*). 2021;10(2):95.

doi: 10.3390/biology10020095

33. Dransfield M, Rowe S, Vogelmeier CF, *et al*. Cystic fibrosis transmembrane conductance regulator: Roles in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2022;205(6):631-640.

doi: 10.1164/rccm.202109-2064TR

34. Besharati S, Owlia P. Evaluation of biofilm production capacity in *Salmonella* isolated from chicken meat in Tehran municipally daily fruit and vegetable markets. *Daneshvar Med*. 2020;28(1):62-72.

35. Besharati S, Farnia P, Farnia P, Ghanavi J, Velayati AA. Investigation of the hypothesis of biofilm formation in coronavirus (COVID-19). *Biomed Biotechnol Res J (BBRJ)*. 2020;4(Suppl 1):S99-S100.

doi: 10.4103/bbrj.bbrj_126_20

36. Besharati S, Soleimani N, Rahbar M. Evaluation of the prevalence of Integron 1, 2 and biofilm formation in clinical isolates of *Pseudomonas aeruginosa* in Tehran, 2024. *J Isfahan Med Sch*. 2025;43:125-134.

doi: 10.48305/jims.v43.i805.0125

37. Besharati S, Owlia P, Sadeghi A, *et al*. Frequency, antibiotic resistance and serogroups of *Salmonella* among chicken meat specimens in Tehran, Iran. *Daneshvar Med*. 2020;27(4):1-10.

doi: 10.1007/s11032-023-01398-w

38. Yang R, Fu D, Liao A. The role of complement in tumor immune tolerance and drug resistance: A double-edged sword. *Front Immunol*. 2025;16:1529184.

doi: 10.3389/fimmu.2025.1529184

39. Chow A, Perica K, Klebanoff CA, Wolchok JD. Clinical implications of T cell exhaustion for cancer immunotherapy. *Nat Rev Clin Oncol*. 2022;19(12):775-790.

doi: 10.1038/s41571-022-00689-z

40. Zhang G, Wang J, Zhao Z, *et al*. Regulated necrosis, a proinflammatory cell death, potentially counteracts pathogenic infections. *Cell Death Dis*. 2022;13(7):637.

doi: 10.1038/s41419-022-05066-3

41. Gao D, Gao W, Zhai Z, Zhu W. Immune mechanisms and novel therapies for idiopathic pulmonary fibrosis. *Pharm Sci Adv*. 2024;2:100030.

doi: 10.1016/j.pscia.2023.100030

42. Ahmed R, Zaman T, Chowdhury F, *et al*. Single-cell RNA sequencing with spatial transcriptomics of cancer tissues. *Int J Mol Sci*. 2022;23(6):3042.

doi: 10.3390/ijms23063042

43. Pelaia C, Tinello C, Vatrella A, De Sarro G, Pelaia G. Lung under attack by COVID-19-induced cytokine storm: Pathogenic mechanisms and therapeutic implications. *Ther Adv Respir Dis*. 2020;14:1-9.

doi: 10.1177/1753466620933508

44. Hsu RJ, Yu WC, Peng GR, *et al*. The role of cytokines and chemokines in severe acute respiratory syndrome coronavirus 2 infections. *Front Immunol*. 2022;13:832394.

doi: 10.3389/fimmu.2022.832394

45. Stegeman SK, Kourko O, Amsden H, *et al*. RNA viruses, toll-like receptors, and cytokines: The perfect storm? *J Innate Immun*. 2025;17:126-153.

doi: 10.1159/000543608

46. Lu T, Yan H, Luo J, Wang S, Xia Y, Xu X. Elevated thrombosis-related biomarkers as predictors of disease severity and mortality in patients with severe fever with thrombocytopenia syndrome. *BMC Infect Dis*. 2025;25:235.

doi: 10.1186/s12879-025-10574-6

47. Krishnamachary B, Cook C, Kumar A, Spikes L, Chalise P,

Dhillon NK. Extracellular vesicletors of disease severity and mortality in patients with severe fever with thrombocytopenia syndrome. *J Extracell Vesicles*. 2021;10(9):e12117.

doi: 10.1002/jev2.12117

48. Ramaswamy A, Brodsky NN, Sumida TS, *et al*. Immune dysregulation and autoreactivity correlate with disease severity in SARS-CoV-2-associated multisystem inflammatory syndrome in children. *Immunity*. 2021;54(5):1083-1095.e7.

doi: 10.1016/j.immuni.2021.04.003

49. Mohite P, Yadav V, Pandhare R, *et al*. Revolutionizing cancer treatment: Unleashing the power of viral vaccines, monoclonal antibodies, and proteolysis-targeting chimeras in the new era of immunotherapy. *ACS Omega*. 2024;9(7):7277-7295.

doi: 10.1021/acsomega.3c06501

50. Paudyal B, McNee A, Rijal P, *et al*. Low dose pig anti-influenza virus monoclonal antibodies reduce lung pathology but do not prevent virus shedding. *Front Immunol*. 2021;12:790918.

doi: 10.3389/fimmu.2021.790918

51. Li N, Parkes JE, Spathis R, *et al*. The effect of immunomodulatory treatments on anti-dystrophin immune response after AAV gene therapy in dystrophin deficient mdx mice. *J Neuromuscul Dis*. 2021;8(s2):S325-S340.

doi: 10.3233/JND-210706

52. Xu C, Hao M, Zai X, *et al*. A new perspective on gut-lung axis affected through resident microbiome and their implications on immune response in respiratory diseases. *Arch Microbiol*. 2024;206(3):107.

doi: 10.1007/s00203-024-03843-6

53. Song Z, Meng Y, Fricker M, Tian H, Tan Y, Qin L. The role of gut-lung axis in COPD: Pathogenesis, immune response, and prospective treatment. *Heliyon*. 2024;10(9):e30612.

doi: 10.1016/j.heliyon.2024.e3061

54. De Oliveira GLV, Oliveira CNS, Pinzan CF, De Salis LVV, Cardoso CRB. Microbiota modulation of the gut-lung axis in COVID-19. *Front Immunol*. 2021;12:635471.

doi: 10.3389/fimmu.2021.635471

55. Loera-Muro A, Guerrero-Barrera A, Tremblay DNY, Hathroubi S, Angulo C. Bacterial biofilm-derived antigens: A new strategy for vaccine development against infectious diseases. *Expert Rev Vaccines*. 2021;20(4):385-396.

doi: 10.1080/14760584.2021.1892492

56. Worley MJ. Immune evasion and persistence in enteric bacterial pathogens. *Gut Microbes*. 2023;15(1):2163839.

doi: 10.1080/19490976.2022.2163839

57. Johnston SL, Goldblatt DL, Evans SE, Tuvim MJ, Dickey BF. Airway epithelial innate immunity. *Front Physiol*. 2021;12:749077.

doi: 10.3389/fphys.2021.749077

58. Paradis T, Bègue H, Basmaciyan L, Dalle F, Bon F. Tight junctions as a key for pathogens invasion in intestinal epithelial cells. *Int J Mol Sci*. 2021;22(5):2506.

doi: 10.3390/ijms22052506

59. Ishihara N, Tanaka M, Namba K, *et al*. Long-term exposure to urban particulate matter exacerbates mortality after ischemic stroke in mice. *J Toxicol Sci*. 2025;50(3):147-159.

doi: 10.2131/jts.50.147

60. Hu D, Jia X, Cui L, *et al*. Exposure to fine particulate matter promotes platelet activation and thrombosis via obesity-related inflammation. *J Hazard Mater*. 2021;413:125341.

doi: 10.1016/j.jhazmat.2021.125341

61. Koul A, Bawa RK, Kumar Y. Artificial intelligence techniques to predict the airway disorders illness: A systematic review. *Arch Computat Methods Eng*. 2023;30(2):831-864.

doi: 10.1007/s11831-022-09818-4

62. Yan C, Wang L, Lin J, *et al*. A fully automatic artificial intelligence-based CT image analysis system for accurate detection, diagnosis, and quantitative severity evaluation of pulmonary tuberculosis. *Eur Radiol*. 2022;32:2188-2199.

doi: 10.1007/s00330-021-08365-z

63. Mettelman RC, Allen EK, Thomas PG. Mucosal immune responses to infection and vaccination in the respiratory tract. *Immunity*. 2022;55(5):749-780.

doi: 10.1016/j.immuni.2022.04.013

64. Fraser R, Orta-Resendiz A, Mazein A, Dockrell DH. Upper respiratory tract mucosal immunity for SARS-CoV-2 vaccines. *Trends Mol Med*. 2023;29(4):255-267.

doi: 10.1016/j.molmed.2023.01.003

65. Jung M, Dourado M, Maksymetz J, *et al*. Cross-species transcriptomic atlas of dorsal root ganglia reveals species-specific programs for sensory function. *Nat Commun*. 2023;14(1):366.

doi: 10.1038/s41467-023-36014-0

66. Mogilenko DA, Shpynov O, Andhey PS, *et al*. Comprehensive profiling of an aging immune system reveals clonal GZMK+ CD8+ T cells as conserved hallmark of inflammaging. *Immunity*. 2021;54(1):99-115.e12.

doi: 10.1016/j.immuni.2020.11.005