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REVIEW

Chronic Diseases and Translational Medicine

# Advances in immune response to pulmonary infection: Nonspecificity, specificity and memory

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## Abstract

The lung immune response consists of various cells involved in both innate and adaptive immune processes. Innate immunity participates in immune resistance in a nonspecific manner, whereas adaptive immunity effectively eliminates pathogens through specific recognition. It was previously believed that adaptive immune memory plays a leading role during secondary infections; however, innate immunity is also involved in immune memory. Trained immunity refers to the long-term functional reprogramming of innate immune cells caused by the first infection, which alters the immune response during the second challenge. Tissue resilience limits the tissue damage caused by infection by controlling excessive inflammation and promoting tissue repair. In this review, we summarize the impact of host immunity on the pathophysiological processes of pulmonary infections and discuss the latest progress in this regard. In addition to the factors influencing pathogenic microorganisms, we emphasize the importance of the host response.

**KEYWORDS**

adaptive immunity, innate immunity, lung infection, trained immunity

## Highlights

- Innate and adaptive immune responses constitute the basic mechanism of lung anti-infection immunity.
- The classical adaptive immune response confers long-term and pathogen-specific protection.
- Trained immunity enhances inflammatory and antimicrobial properties in a nonspecific manner.

## 1 | INTRODUCTION

Lung infections impose an extremely large economic and health burden worldwide. For seniors, the mortality risk of pneumonia hospitalization is higher than that of other common causes of hospitalization.[1,2] A study of the 2019 Global Burden of Diseases (GBD) showed that lung infections affected 489 million people globally, and the elderly are the most affected population.[3] In particular, the current COVID-19 pandemic has seriously threatened public health. However, the pathogenesis of lung injury, including the role of cell-related immune responses in acute/chronic lung infections, has not been fully elucidated. Although the widespread use of antibiotics has greatly reduced the mortality rate of pulmonary infections in recent years, drug-resistant bacteria pose great challenges to clinical anti-infective therapies. Many studies on lung infections have focused

on clearing pathogens via antibiotics and host resistance. Although lung infections are caused by microorganisms, the host immune response is the driving factor for disease development. In this review, we summarize the impact of host immunity on the pathophysiological processes of pulmonary infections and the latest progress. In addition to the factors influencing pathogenic microorganisms, we emphasize the importance of the host response. Supplementing and updating the relevant knowledge can assist in the improvement of clinical treatment so that patients with lung infections can receive broader benefits.

## 2 | INFECTION AND COLONIZATION OF PATHOGENS

Pathogenic examination of pulmonary infections is important for clinical real-time individualized antibiotic treatment and the reduction of antibiotic resistance. Pathogenic microorganisms in community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP) differ substantially. Various pathogens, such as *Streptococcus pneumoniae*, respiratory viruses, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, and *Legionella pneumophila*, are common in CAP.[4] However, the most common microorganisms in HAP are *Staphylococcus aureus*, Enterobacterales, non-fermenting gram-negative bacilli, and Acinetobacter.[5] In many cases, the results of etiology do not represent the source of infection because the responsible pathogens are often opportunistic microorganisms. Most individuals carrying opportunistic pathogens do not develop pneumonia or any other serious illnesses. The pathophysiological mechanisms underlying lung infections are gradually being elucidated. The modes of pathogen transmission include direct and indirect contact. In most cases, these viruses are transmitted between individuals in the form of droplets or aerosols. When the bacteria enter the human body, they can escape the clearance of the host by changing their own antigens, expressing the mimic of the host or high viscosity, and then attach to airway epithelial cells (AECs).[6–8] The occurrence of bacterial pneumonia is mostly due to the inhalation of microorganisms from the nasopharynx into the lower respiratory tract. Infection occurs when host defenses are impaired (such as barrier integrity) or the host is exposed to a large number of pathogens or highly invasive and virulent microorganisms. Individuals who have previously been infected with viruses or have chronic lung disease are more likely to advance from colonization to lung infection.[9]

Changes in pulmonary microecology have also been associated with infection. Studies have shown that the main bacteria in the lower respiratory tract of healthy individuals include *Prevotella*, *Streptococcus*, *Veillonella*, *Fusobacterium*, and *Haemophilus* spp. In the case of pulmonary infection, the composition and diversity of the microbiota also changes, which is related to the immune response.[10] The mechanism by which the pulmonary microbiota affects airway immunity has been partially elucidated. Nucleotide-binding oligomerization domain-containing (NOD)-like receptors are activated by bacteria in the upper airway, which increase the production of GM-CSF in the lungs through interleukin-17A and improve resistance to pneumonia.[11]

Immune resistance and tissue resilience are two seemingly opposing processes, and their balance is crucial for maintaining lung homeostasis during microbial colonization or infection. Immune resistance refers to the elimination of invasive pathogens, while tissue resilience reduces host tissue damage by limiting excessive immunity or promoting tissue repair, which directly affects the progress and outcome of pulmonary infection.[12] Therefore, it is very important to fully understand the action pathways and mechanisms of the two processes to maintain host homeostasis.

## 3 | NONSPECIFIC IMMUNITY: INNATE IMMUNITY

For pathogen containment, the immune response within the respiratory tract follows an ordered stepwise program of engagement with distinct tiers of defense. The innate immune system, which is the first line of defense against pathogenic microorganisms, reacts within minutes to hours of respiratory infection. Local sensor cells first detect invading microorganisms and secrete chemical attractants to recruit neutrophils. They then secrete cytokines to warn the lymphocytes residing in the lung, including congenital lymphocytes (ILCs), tissue resident memory T (TRM) cells, and congenital lymphocytes and natural killer (NK) cells. These immune cells further activate effector cells to eliminate pathogens via phagocytosis or expression of foreign particles.[13]

### 3.1 | AECs

Anatomical barriers represent the first line of defense against lung infections. Lung epithelial cells are distributed in the upper and lower respiratory tracts.[14] The surfactant proteins (SP) synthesized by alveolar epithelial type II cells can directly inhibit microorganisms in the alveoli,[15] and the mucociliary system plays an important role in clearing pathogens in the upper respiratory tract and lungs. In patients with cystic fibrosis, mucus fluidity is reduced due to CFTR mutations, and the lung infection rate is significantly increased,[16] emphasizing the importance of mucus in lung immunity. The branched bronchial trees provide additional defense mechanisms by preventing large particles from entering the lower airway.

In addition to constituting a physical defense mechanism, epithelial cells can respond to infectious stimuli and undergo transcriptional remodeling when exposed to invasive pathogens. Therapeutic stimulation of the lungs with inhaled Toll-like receptor (TLR) agonists can protect mice from fatal pneumonia and target the destruction of TLR signal transduction in the lung epithelium, leading to the complete disappearance of this protective effect.[17] Myeloid differentiation factor 88 (MyD88) is an essential factor for pulmonary immune resistance. It is a central adaptor protein in most TLR signaling pathways. MyD88 expression by epithelial cells is sufficient to generate a rapid and protective innate immune response following intranasal infection with *P. aeruginosa*, indicating that pulmonary epithelial cells are necessary effectors for inducing resistance.[18] Further research shows that pulmonary epithelial cells lead to efficient neutrophil recruitment and enhanced bacterial clearance by restoring inflammatory cytokine and antimicrobial peptide production.[19] IL-17 can trigger neutrophil recruitment by stimulating epithelial cells to secrete antimicrobial proteins and CXC chemokines. IL-22 can promote the repair of lung injury by stimulating the proliferation of epithelial cells.[20] Type II alveolar cells (AT2s) can express high levels of MHC II, but their capacity is relatively weak compared to professional antigen-presenting cells, which position AT2s to contribute to lung adaptive immune responses in a controllable way without causing excessive inflammatory damage.[21]

## 3.2 | Alveolar macrophages

AMs are phagocytes that reside in the lower respiratory tract. This is the first line of leukocyte antibacterial defense. Experiments with GFP-expressing chimeric mice strongly support that the lifespan of AMs approaches the mouse lifespan.[22] AMs are extremely diverse and play an important role in immune resistance and tissue resilience. In general, macrophages remove environmental debris, excessive surfactants, apoptotic cells, and other harmless substances.[23] In an infected environment, AMs play a significant role in plasticity, transforming from an anti-inflammatory cell to a regulatory center of immune activity. Macrophages contain many pattern recognition receptors. After sensing pathogens, AMs directly promote immune resistance by ingesting and phagocytosing microorganisms.[24] The phagocytosed pathogens can be killed by the reactive oxygen species in the cells,[25] or cleared by the apoptosis of AM cells.[26] AMs can also present processed antigens, in the form of antigenic peptide MHC molecular complexes, to $CD4^+$ T cells and $CD8^+$ T lymphocytes, to remove antigens through immune inflammatory reactions and cytotoxic effects. In contrast, the death of AMs through non-apoptotic pathways (such as necrosis) weakens the antibacterial defense during pneumonia.[27] The AMs' antimicrobial ability is sufficient to control the pathogen load under normal conditions. When the pathogen is too toxic or too numerous, AMs need to stimulate other innate immune cells in the lung via NF-κB, interleukin (IL) 6 and chemokines. The first burst of these cytokines during pneumonia originates from alveolar macrophages and subsequently triggers rapid and coordinated responses to local infection.[28]

## 3.3 | Dendritic cells (DCs)

DC are important antigen-presenting cells that capture and present exogenous antigens in $CD8^+$ T lymphocytes. Lung DCs are heterogeneous, and the phenotypic heterogeneity of lung DCs are associated with specialized immune functions.[29] Two main DC subsets have been described in lungs under healthy homeostatic conditions. They were distinguished based on the expression levels of CD11b and CD103. $CD103^-$ DC specifically presents innocuous Ag to $CD4^+$ T cells, while $CD103^+$DC specifically presents Ag to $CD8^+$ T cells.[30] Another study also underscored a specific role for Batf3-dependent DCs in regulating priming and expansion of effector $CD8^+$ T cells necessary for host resistance against acute respiratory vaccinia virus infection.[31] In mice infected with *Pseudomonas aeruginosa*, the concentration of DC increased significantly, accompanied by the increased expression of CD80 and CD86 and the early secretion of IL-12, which supports the idea that DCs are involved in skewing of the Th1/Th2 balance in CF.[32] DC also plays a role in immunosuppression. Autocrine IL-10 signaling promotes DC type-2 activation and suppresses immune resistance, and leads to persistent cryptococcal infection in the lungs of mice.[33]

## 3.4 | Innate lymphoid cells (ILCs)

ILCs, identified in the lungs of humans and mice, are the counterparts of T cells that regulate immune responses by producing effector cytokines and affect the function of other congenital and adaptive immune cells.[34,35] The abundance of these cells is relatively low, but they are abundant on the surface of the lung mucosa. ILCs are divided into three categories according to their ability to secrete type 1, 2, and 17 cytokines, namely ILC1, ILC2, and ILC3, which are consistent with the functions of Th1, Th2, and Th17 adaptive lymphocytes.[36] ILC1s can be activated by IL-12, specifically express T-bet, and produce tumor necrosis factor (TNF) and interferon (IFN)-γ, which play a key role in promoting the clearance of intracellular pathogens. Due to the local differentiation of lung ILC precursors into ILC1-like cells during *Mycobacterium tuberculosis*

(Mtb) infection, the bacterial load decreased significantly after Mtb attack, which proved the protective ability of ILC1-like cells during Mtb infection.[37] ILC2s produce the effector cytokines IL-4, IL-5, IL-9, IL-13, and amphiregulin, and rapidly respond to parasites.[36] Using single-cell RNA sequencing, researchers identified a transcriptionally distinct ILC2 subset that showed enrichment for wound-healing signature genes and the transcription factor BATF. BATF promotes the proliferation and function of ILC2s, and restricts their plasticity during infection with influenza virus.[38] ILC3s play a protective role in lung infection by secreting IL-17 and IL-22. IL-17 has been proven to be critical in resisting extracellular bacteria and fungi. Furthermore, the co-regulated cytokine IL-22 plays a role in the process of tissue repair, which can promote the epithelial integrity of intestinal or lung barrier surfaces after inflammatory injury.[39] It is clear that ILCs are important members of the innate immune response against bacterial pneumonia.[40]

Unconventional T cells are another group of lymphocytes that promote lung innate immunity in addition to ILCs.[41] Mucosal-associated invariant T (MAIT) cells are innate-like T lymphocytes that are abundant in the respiratory mucosa[42] that play a significant role in immune defense against microbial infections. MAIT cells can be activated by IL-18 and IFN-α, and function as innate sensors of inflammation and viral infection.[43] Invariant natural killer T (iNKT) cells can be activated by the IL-1β and IL-23 provided by infected DCs and recognize lipid antigens presented by the MHC-like molecule CD1d.[44] The activated iNKT cells rapidly produce cytokines, such as IL-22, which play a positive role in controlling inflammation damage.[45]

## 3.5 | Natural killer (NK) cells

NK cells are a type of innate lymphocytes enriched in lung tissue that play an important role in the innate immune process against both viral and bacterial pathogens.[46,47] In the mouse model infected by cowpox virus, NK cells in the lungs were activated and produced IFN-γ before the arrival of the CD8 T cells, which highlights the importance of NK cells in the T cell-dependent control of VACV in the respiratory tract.[48] Mice lacking the NK cell activating receptor NCR1 (NKp46) had an increase in lung bacterial load and mortality with *S. pneumoniae* infection.[49] Similar results were found in NK-depleted mice cells with *Klebsiella pneumoniae* infection, where a subset of lung NK cells produced IL-22, indicating that the production of IL-22 may be important for NK cells to defend against bacteria.[50] Researchers also found that the NK cell response was impaired in the airway of lungs affected by influenza, which failed against subsequent *S. aureus* bacterial infection, while adoptive transfer of naive NK cells to the airway restored the antibacterial ability of prior influenza-infected mice.[51] However, the rapid and powerful immune response mediated by NK cells may sometimes cause excessive inflammation. Depletion of NK cells in vivo with anti-asialo GM1 or anti-NK1.1 reduced mice mortality from influenza infection and recovered the body weight of mice by alleviating lung immunopathology.[52] These findings reveal the dual role of NK cells in influenza infection.

## 3.6 | Neutrophils

Neutrophils, which are sparse in the airspaces of uninfected lungs, are the earliest and most abundantly recruited leukocytes. The average lifespan of circulatory neutrophils is 5.4 days in humans under physiological conditions.[53] Neutrophils exert a wide range of antibacterial activities against both intra- and extracellular pathogens. The depletion or dysfunction of neutrophils leads to the aggravation of mice infected with *S. pneumoniae* or *S. aureus*, indicating their importance in the context of lung infections.[54,55] There are three means of neutrophil-mediated killing. The first is phagocytosis, through which ingested organisms are killed by exposure to reactive oxygen species and acidity. The second is degranulation, in which granules release toxic factors into the phagosome or extracellular space. Toxic factors, including cathepsins, gelatinase B (MMP9), myeloperoxidase (MPO), defensins, and other antimicrobial proteins can destroy the structure of microorganisms and play antibacterial roles. Neutrophil extracellular traps (NETs) play an important role in the early control of lung fungal infection.[56,57]

Upon infection, activated neutrophils release various inflammatory chemokines and cytokines to recruit additional immune cells. Acute respiratory distress syndrome (ARDS) induced by severe virus infection exhibited unusually high levels of CXCL10 that further promoted oxidative burst and chemotaxis of inflammatory neutrophils through autocrine signaling, leading to fulminant lung inflammation.[58] In addition, neutrophils also affect the function of other immune cells. Neutrophils guide iNKT cells from the lung vasculature via CCL17, which is essential for defending mice against pneumococcal pneumonia. Impairing iNKT cell recruitment by blocking CCL17 can increase the susceptibility to *S. pneumoniae* infection in mice.[59] Therefore, neutrophils are important for acute lung inflammation and play a central role in immune resistance.

## 3.7 | Recruited macrophages

In contrast to AMs, a distinct subset of recruited macrophages derived from the bone marrow plays an

indispensable role in lung innate immunity. These cells are distinguished from AMs by the high expression of Ly6C.[60] Chemokine CCL2 is the main signal to recruit monocytes into the alveoli.[61] It has been shown that the expression level of CCL2 is inversely proportional to the bacterial load in the lungs of streptococcal infected mice, supporting an essential role for recruited macrophages in immune resistance in lungs.[62] Similarly, recruited monocytes or macrophages can also enhance the accumulation of other immune cells. Inflammatory monocytes are rapidly recruited to the lungs of *K. pneumoniae*-infected mice and produce TNF, which markedly increases the frequency of IL-17-producing ILCs. Monocyte-mediated bacterial uptake and killing are enhanced by IL-17A production via ILCs.[63] Thus, the consistency of recruited monocytes with other immune cells has become a key determinant of immune resistance. However, a dysregulated macrophage response can damage the host, such as macrophage activation syndrome induced by severe infections.[64] High-dose pH1N1 infection induces excessive pro-inflammatory responses, such as sustained neutrophil infiltration, imbalanced macrophage polarization, and earlier and dysregulated cytokine storm, which are associated with the progression of acute lung injury.[65]

### 3.8 | Platelets

Although the role of platelets in blood coagulation is well recognized, its function in innate immunity cannot be ignored.[66] In the mouse model of pneumonia-derived sepsis, thrombocytopenia was found to be associated with strongly impaired survival during pneumonia-derived sepsis, which was proportional to the extent of platelet depletion. Low platelet counts in whole blood enhanced *Klebsiella*-induced cytokine release, indicating the essential role of platelets in host defense.[67] In addition, their related platelet GTPase and adhesion molecules promote pulmonary neutrophil recruitment and host defense.[68] The alpha-granules in human blood platelets contain a number of antibacterial proteins, which are bactericidal for a variety of bacteria.[69] However, studies have also found that excessive platelet activation leads to excessive inflammation and lung injury.[68,70]

## 4 | SPECIFIC IMMUNITY: ADAPTIVE IMMUNITY

### 4.1 | Cellular immunity

T cells are divided into two subsets: $CD4^+$ T helper cells and $CD8^+$ cytotoxic T cells. Naïve $CD4^+$ T cells are activated by DCs that present antigens and subsequently differentiate into different subsets. Th1 has antiviral characteristics that trigger cell-mediated immune responses by activating other immune cells.[71] The predominance of the Th1 response against *Aspergillus fumigatus* was also demonstrated,[72] representing protective adaptive immunity. Aberrant inflammation, caused by Th2 cells, is the most important pathological process in asthma. Th2 cytokines, including interleukin (IL)–5, IL-4, and IL-13, promote inflammation.[73] Th2 cells also impose significant influence on antibody production and allergic reactions, which seem to play a non-protective role during lung infection. For example, heightened Th2 reactivity was found in cystic fibrosis patients that developed allergic bronchial-pulmonary aspergillosis (ABPA) that could be reduced by vitamin D treatment.[74] It is now well established that Th17 lymphocytes associate with myriad immune-mediated inflammatory diseases.[75] Th17 cells as important pro-inflammatory cells, induce epithelial cells to produce antimicrobial peptides, chemokines, and granulocyte growth factors to promote neutrophil accumulation in airways.[76] Th17 can also promote a positive feedback loop that activates innate immune cells, confirming their role in emphysema pathogenesis.[77] Treg cells play a role in immunosuppression, regulating the intensity of the inflammatory reaction and promoting tissue repair. Th cells are essential contributors to B cell proliferation, differentiation, and high-affinity antibody synthesis, and are required for germinal center formation and maintenance, which is critical for humoral immunity.[78] Cellular immunity is critical for early defenses against COVID-19 compared with humoral immunity.[79] Special pathogen infection may cause T cell exhaustion. The peripheral blood mononuclear cells (PBMC) of patients with *Mycobacterium avium* complex-induced lung disease (MAC-LD) display a weak response to non-tuberculous mycobacteria (NTM), with a decreased production of IFN-γ. The expression of PD-1 and apoptotic markers, such as TIM-3, are increased in $CD4^+$ and $CD8^+$ T cells.[80]

### 4.2 | Humoral immunity

B lymphocytes are the main effector cells of humoral immunity and can neutralize antigens by producing specific antibodies. For instance SARS-CoV-2 infection induces the generation of potent neutralizing antibodies (nAbs) against the spike (S) protein.[81] The development of humoral immunity depends on the activation of antigen-specific B cells, which leads to the formation of germinal centers and differentiation into long-lived plasma cells or memory B cells.[82] Some antibodies can neutralize microorganisms in a similar manner to those that initially induce humoral immunity. The increase in antibodies against some of these pneumococcal antigens in vaccinated mice can improve the defense against pneumonia caused by non-vaccine pneumococcal serotypes.[83]

# 5 | IMMUNE MEMORY

## 5.1 | Specific immune memory

Immunological memory is a key feature of the adaptive immune system. This is the basis for the effectiveness of vaccines against specific infections.[84] Localized depots of immune memory were found in the respiratory tract, which specifically protect the lungs from pathogenic microorganism infections. Researchers have reported from examination of SARS-CoV-2 seropositive organ donors that $CD4^+$ T, $CD8^+$ T, and B cell memory generated in response to infection is present in the bone marrow, spleen, lung, and multiple lymph nodes (LNs) for up to 6 months after infection.[85] Resident memory T (TRM) cells, characterized by the expression of the C-type lectin CD69 or the integrin CD103, were observed in multiple sites, including the lungs, intestines, skin, vaginal mucosa, liver, intestines, and lymph nodes.[86,87] The lung TRM cells can be generated from site-specific infection and are specifically retained within the lung, which is different from the memory T cells isolated from the spleen.[88,89] In mice with lobar pneumonia, $CD4^+$ TRM cells were confined to the previously infected lobe, rather than dispersed throughout the lower respiratory tract. Pneumonia protection was also confined to that immunologically experienced lobe.[90] The influenza-specific lung-resident memory $CD4^+$ T cells serve as in situ protectors for respiratory viral challenge, mediating enhanced viral clearance and survival to lethal influenza infection.[91] Tuberculosis-specific parenchymal $CD4^+$ T cells displayed better control of infection compared with their intravascular counterparts.[92] $CD8^+$ TRM from human lungs is different from peripheral $CD8^+$ effector memory cells. They have different transcriptomes, including the mRNA expression of effector molecules. This means that lung TRM cells are not only better positioned in the anatomy but also react more quickly during lung infection.[93] Influenza-specific $CD8^+$ T cells in the BAL fluid were highly enriched after challenge. However, $CD8^+$ TRM cells in the human lung display innate-like gene and protein expression that demonstrates blurred divisions between innate and adaptive immunity.[94] The inducible bronchus-associated lymphoid tissue (iBALT) forms in the lungs post infection or inflammation for months.[95] The iBALT is the source of memory B cells and plasma cells that provide whole-body protection, and is also the site for producing local antibodies.[96] Lung-resident memory B cells (MBCs) have also been identified recently. Two transcriptionally distinct subsets of MBCs colonize the peribronchial niche of the lung after infection. These cells differentiate into plasma cells with short lifespans and produce high-affinity antibodies. They can also provide long-term protection with increased affinity and breadth by re-entering the germinal center.[97] It has been reported that potential memory NK cells were be induced during the first 6 months after the use of influenza vaccines, which increase antigen-specific recall IFN-γ responses.[98] Interestingly, liver rather than lung NK cells from influenza virus-infected mice possess a memory phenotype and protect mice against secondary influenza virus infection.[99] Thus, lung immune memory cells protect against diverse types of respiratory pathogens and provide more efficient immune defense.

## 5.2 | Nonspecific immune memory: Trained immunity

The microecology and immune environment of lungs with prior infections differ from those of naive lungs. It was previously believed that the innate immune response is rapid and activates adaptive immunity at the time of the initial infection. During the secondary infection, the scale of the innate immune response was reduced, and the adaptive immune response (memory T/B cells) was more rapid and effective.[100] It was also thought that innate immune responses are nonspecific and lack immunological memory. However, plants and invertebrates lacking adaptive immune responses survive re-infection with pathogens; in mammals, cross-protection between infections is independent of T and B cells.[101] This suggests that, similar to acquired immune memory, the activation of innate immune cells can also result in enhanced nonspecific responsiveness to subsequent triggers. This process has been called "trained immunity," a de facto innate immune memory.[102,103] Bacillus Calmette-Guérin (BCG) is the most widely studied vaccine for induced training immunity. It was found that vaccinia and BCG vaccinations were associated with better long-term survival, which could not be explained by specific protection.[104] BCG vaccination in healthy volunteers led not only to a four- to seven-fold increase in the production of IFN-γ, but also to a twofold enhanced release of monocyte-derived cytokines, in response to unrelated bacterial and fungal pathogens.[105] Another study showed that BCG vaccination induced genome-wide epigenetic reprograming of monocytes and protected against experimental infection with an attenuated yellow fever virus vaccine strain.[106] Besides monocytes, BCG-educated hematopoietic stem cells (HSCs) also generate epigenetically modified macrophages that provide significantly better protection against virulent *M. tuberculosis* infection than naive macrophages.[107] Adaptive T cells can render innate macrophage memory via IFN-γ production, and memory macrophages mediate trained antibacterial immunity via enhanced neutrophilia.[108] A recent study has described that at one-month post-influenza following viral clearance and clinical recovery, mice could better protect themselves from *S. pneumoniae* infection due to monocyte-derived AMs that promote increased levels of IL-6.[109] Although NK cells traditionally have been

classified as cells of the innate immune system, they share many similarities with cytotoxic T lymphocytes. NK cells bearing the virus-specific Ly49H receptor proliferate massively in mice infected with cytomegalovirus (CMV) and rapidly degranulate and produce cytokines upon reactivation.[110] The emergence of diverse subsets of human NK cells that selectively lack the expression of signaling proteins after human cytomegalovirus (HCMV) infection has also been described. These epigenetically unique adaptive NK cell subsets diversify in response to viral infection and have distinct functional capabilities compared to canonical NK cell subsets.[111] Trained immunity induces heterologous protection against infections through epigenetic, transcriptional, and functional reprogramming of innate immune cells. The signal from the adaptive to the innate immune systems also generates a trained immunity key for protection from re-infection (Figure 1).

## 6 | TISSUE RESILIENCE

Resistance is the ability to reduce the pathogen burden via the response of the immune system and downstream events. Excessive inflammation can cause fatal tissue damage. Tissue resilience is another defense strategy that limits injury resulting from all aspects of infection.

AECs and the mucosal layer continually defend against infection at the earliest stages, averting leukocyte recruitment and the subsequent inflammatory response. In a study on long-term exposure to *A. fumigatus*, Treg cells were induced and constrained the function of $CD69^{hi}CD103^{lo}CD4^{+}$ TRM cells. The absence of Tregs leads to the deterioration of chronic lung inflammation and the aggravation of fibrosis.[112] In addition to inhibiting the lung tissue damage of other immune cells, another study found that Tregs can promote tissue repair of lung injury by producing AREG, which is dependent on the inflammatory mediators IL-18 and IL-33 in the early stage of influenza virus infection and is independent of its immunosuppressive effect.[113] Researchers have found ILCs aggregation in the lungs of mice after influenza virus infection. However, the depletion of ILCs leads to airway epithelial damage and a decline in lung function. Through the analysis of the transcriptome of ILCs, it was found that a large number of AREG genes were enriched, which played an important role in tissue repair, further confirming the role of ILCs in maintaining the integrity of airway epithelium and homeostasis of the tissue environment.[114] Using real-time alveolar imaging in situ, researchers found that alveolar macrophages were connected to epithelial cells by connexin 43 (Cx43). A calcium wave is used to transmit immunosuppressive signals between these two kinds of cells and inhibit the production of pro-inflammatory factors and neutrophil recruitment in the process of LPS-induced inflammation.[115] Alveolar macrophages expressing TGF-β and

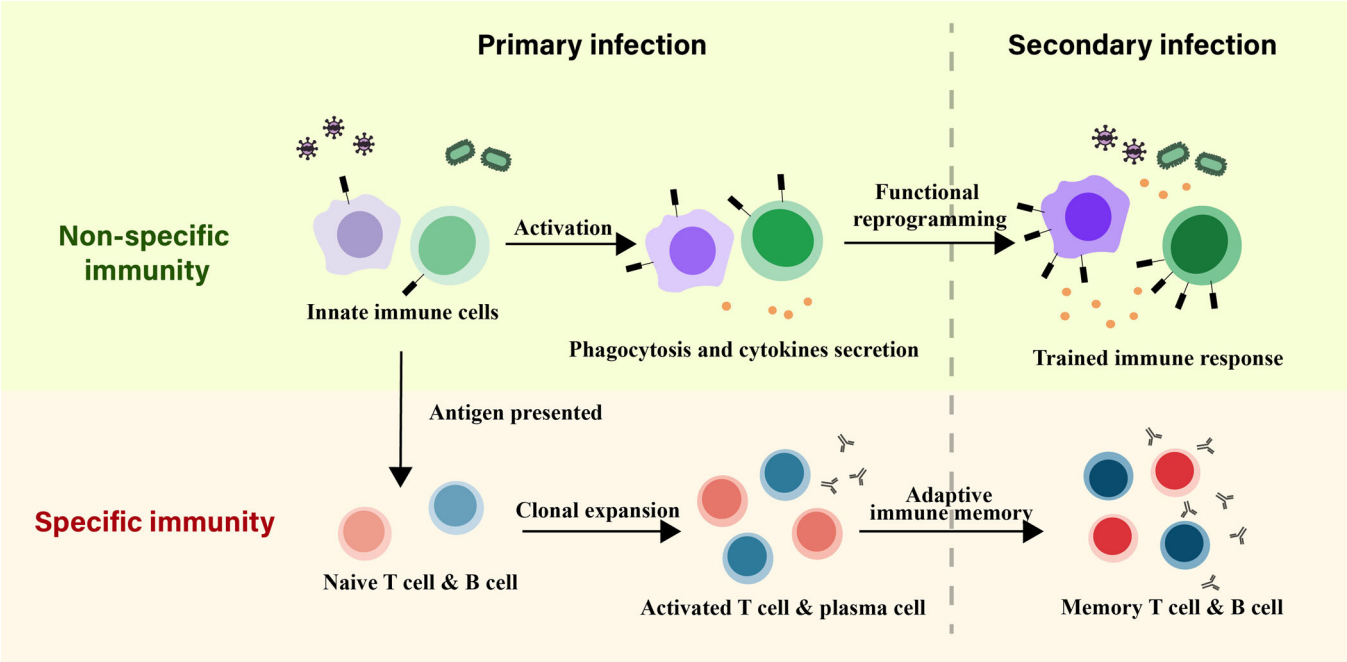


**FIGURE 1** Nonspecific and specific immune responses during primary and secondary infection. The innate immune cells are activated after immune recognition and initiate the innate immune response leading to adaptive immunity stimulation, cytokine secretion, pathogen elimination, and trained immunity. The classical adaptive immune memory involves gene recombination in T and B cells, which confers often long-term and pathogen-specific protection. Trained immunity enhances inflammatory and antimicrobial properties in innate immune cells. Both of them provide protection from re-infection.

retinoic acid can induce naive T cells to express Foxp3 and differentiate into Tregs, so as to further control inflammation.[116] Thus, many cell types enhance intrapulmonary resilience during pneumonia.

## 7 | CONCLUSION

Lung infection is one of the most common infectious diseases; in particular, the coronavirus disease (COVID-19) pandemic has severely threatened public health. The outcome of lung infection is determined by the degree of immune protection and inflammatory damage. The lung immune response consists of various cells involved in both innate and adaptive immune processes. The immune system fights infections through an intercellular signaling network. In addition to specific adaptive immune memory, training immunity as a nonspecific immune memory mediated by innate immune cells, also plays an important role during secondary infection. Immune responses to respiratory infections must be strong enough to eliminate the infection but also have mechanisms to limit damage and promote tissue repair to maintain pulmonary homeostasis. Disease development largely depends on the host's immune response, and pathogen characteristics play a less prominent role. It is important to better understand how the body successfully resists respiratory pathogens and protects itself, so that we can recognize and counter deficiencies in these protective pathways.

### AUTHOR CONTRIBUTIONS

The first draft of the manuscript was written by Jianqiao Xu, and the manuscript was revised by Lixin Xie. All authors contributed to the article and approved the submitted version.

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### CONFLICT OF INTEREST STATEMENT

Professor Lixin Xie is a member of Chronic Diseases and Translational Medicine editorial board and is not involved in the peer review process of this article. The remaining author declares no conflict of interest.

### DATA AVAILABILITY STATEMENT

Data availability is not applicable to this article as no new data were created or analyzed in this study.

### ETHICS STATEMENT

This manuscript does not involve human or animal experiments.

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