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Inflammatory mechanisms in the lung

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Abstract

Inflammation is the body's response to insults, which include infection, trauma, and hypersensitivity. The inflammatory response is complex and involves a variety of mechanisms to defend against pathogens and repair tissue. In the lung, inflammation is usually caused by pathogens or by exposure to toxins, pollutants, irritants, and allergens. During inflammation, numerous types of inflammatory cells are activated. Each releases cytokines and mediators to modify activities of other inflammatory cells. Orchestration of these cells and molecules leads to progression of inflammation. Clinically, acute inflammation is seen in pneumonia and acute respiratory distress syndrome (ARDS), whereas chronic inflammation is represented by asthma and chronic obstructive pulmonary disease (COPD). Because the lung is a vital organ for gas exchange, excessive inflammation can be life threatening. Because the lung is constantly exposed to harmful pathogens, an immediate and intense defense action (mainly inflammation) is required to eliminate the invaders as early as possible. A delicate balance between inflammation and anti-inflammation is essential for lung homeostasis. A full understanding of the underlying mechanisms is vital in the treatment of patients with lung inflammation. This review focuses on cellular and molecular aspects of lung inflammation during acute and chronic inflammatory states.

Keywords: inflammation, lung, inflammatory mediators, cytokines

Introduction

Immunity involves innate and adaptive systems. Innate immunity is nonspecific and evokes rapid

responses, including inflammation in face of pathogen insults. Adaptive immunity is antigen-specific. It first detects the specific antigen and then mobilizes inflammatory cells to target that particular antigen. The innate and adaptive systems share components and act in concert to defend against pathogens. The lungs are exposed to constant insults from the atmosphere and also to toxic molecules circulating through the pulmonary and bronchial vasculature. Elaborate pulmonary defense mechanisms are needed for survival. These include first-line filtration and removal systems such as the nasal vibrissae, mucociliary escalator, and cough reflex. Secretory immunoglobulin A (IgA) in mucus and surfactant produced by alveolar cells also assist in immunity against pathogens and smaller particles, while resident immune cells within the lung parenchyma await organisms that successfully penetrate the physical barriers. Optimal lung defense requires the coordinated action of multiple cell types.

Defense mechanisms in the lung

The airway epithelium is the first site of contact with inhaled agents. Its epithelial cells secrete a variety of substances such as mucins, defensins, lysozyme, lactoferrin, and nitric oxide, which nonspecifically shield the respiratory tract from microbial attack.¹ The epithelial cells also produce a number of mediators such as reactive oxygen radicals, cytokines (TNF- α , IL-1 β , granulocyte/macrophage colony-stimulating factor [GM-CSF]), and platelet-activating factor to recruit inflammatory cells onto the site of inflammation.² The cytokines stimulate arachidonic acid release from membrane lipids, leading to production of eicosanoids, which further stimulate mucus secretion by goblet cells and tissue inflammation.

Surfactant lies on the surface of alveoli and contains four surfactant proteins (SP A-D). Important for reducing lung surface tension, these proteins play a critical role in surfactant absorption into the alveolar surface. SP-A and SP-D also participate in host defense. They bind bacterial surface molecules, modulate leukocyte activity, and lead to pathogen opsonization.³

IgA secreted by plasma cells forms an additional epithelial protective barrier, which prevents microbial adherence to the epithelial surface⁴ and inhibits certain viral infections (influenza and rotavirus) by interfering with their assembling processes. It also binds to pathogens, causing phagocytosis and antibody-dependent cell-mediated cytotoxicity. Selective IgA deficiency manifests as atopy and recurrent respiratory tract infections. Moreover, patients with COPD have decreased IgA levels in saliva and bronchial secretions.⁵ Immunoglobulin E (IgE) induces immediate type hypersensitivity in the respiratory tract. It produces severe reactions by binding to IgE receptors on the surfaces of mast cells, basophils, eosinophils, and B lymphocytes. Repeat exposure to the same antigen induces degranulation and the release of pro-inflammatory mediators, including histamine, prostaglandins, leukotrienes, and tryptase.⁶ These increase vascular permeability, bronchoconstriction, and inflammatory cell infiltration.

The foregoing pulmonary defenses maintain sterility in the lower respiratory tract, and redundancy in their mechanisms ensures overlapping protection from invading pathogens.

Inflammatory cells

Dendritic cells are antigen-presenting cells (APCs), which stimulate naïve T cell proliferation.

Dendritic cells and macrophages are the first line of defense in recognizing various pathogens. Originating in bone marrow, dendritic cells reach tissues through blood circulation and, in the lung, reside in and below the airway epithelium, the alveolar septa, pulmonary capillaries, and airway spaces.⁷ Once the dendritic cell identifies, ingests, and processes an antigen, it migrates to the lymph nodes and presents the antigen to resident T cells, inducing the immune response.

Macrophages reside in the airways, alveoli, and lung interstitium, or migrate into the lung microvasculature. Their role is essential in modulating acute and chronic inflammatory responses, but although macrophages can proliferate within the lung, their number is not adequate to fight infection.⁸ Macrophage function is augmented by dendritic cells. Together they are capable of phagocytosing bacteria, particulates, and apoptotic cells. However, macrophages are the main source of cytokines, chemokines, and other inflammatory mediators that propagate or suppress the immune response. Following an insult, macrophages and epithelial cells secrete chemokines and cytokines, promoting neutrophil accumulation and local inflammation.⁹

Neutrophils provide second-line defense. They are the first cells to be recruited to sites of infection or injury, and attack fungi, protozoa, bacteria, viruses, and tumor cells. During pulmonary infection, neutrophils migrate out of the pulmonary capillaries and into the air spaces.¹⁰ After phagocytosis, neutrophils kill ingested microbes with reactive oxygen species, antimicrobial proteins (bactericidal permeability-inducing protein and lactoferrin), and degradative enzymes (elastase). Deficits in neutrophil quantity (neutropenia) and quality (chronic granulomatous disease) predispose patients to opportunistic lung infections.

Lymphocytes are found throughout the airway and lung parenchyma. There are two major populations of lymphocytes: thymus-dependent T cells and bone marrow-dependent B cells. T lymphocytes provide cell-mediated immunity, while B lymphocytes produce humoral immune responses by synthesizing antibodies (immunoglobulins). T lymphocytes have two major subsets: CD4⁺ and CD8⁺. CD4⁺ T lymphocytes are also known as helper T cells, which are further subdivided into Th1 and Th2 with different cytokine profiles. Th1 cells drive cellular immunity. Th1 cytokines (interferon gamma, TNF- α) produce the pro-inflammatory responses to fight viruses and other intracellular parasites, and to eliminate cancer cells. Excessive pro-inflammatory responses can lead to uncontrolled tissue damage. Th2 cells drive humoral immunity to up regulate antibody production to fight extracellular organisms. Th2 cytokines (IL-4, IL-5, IL-9, and IL-13) promote IgE and eosinophilic responses in atopy. Excessive Th2 responses will counteract the Th1-mediated anti-microbial actions ([Figure 1](#)). Optimally, a balanced Th1 and Th2 response is suited to the immune challenge, and a dysregulated response is linked to a variety of chronic inflammatory conditions like asthma and chronic bronchitis.¹¹ CD8⁺ T cells are mainly cytotoxic T cells. They secrete molecules that kill infected cell and tumor cells. In addition, there is a natural killer cell (NK cell) subset of T cells with no antigen-specific receptors.¹² Another subset of T cells, named NKT cells, which have the properties of NK cells, are important in combating bacteria, protozoa, and viruses.¹³ Furthermore, there are regulatory cells, which suppress the other lymphocytes. During the immune response, some antigen-activated B cells and T cells differentiate into memory cells, producing long-lasting immunity.

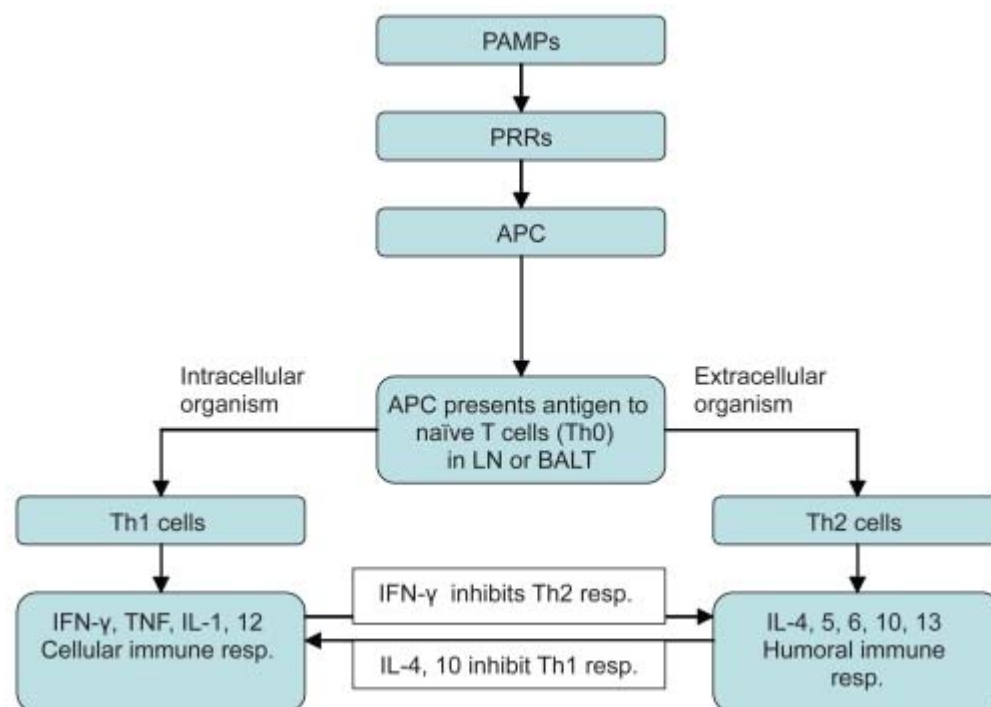


Figure 1

Immune response to lung infections.

Abbreviations: APC, antigen presenting cell; BALT, bronchial-associated lymphoid tissues; LN, lymph nodes; PAMPs, pathogen-associated molecular patterns; PRRs, pattern recognition receptors; resp, response; Th0, naïve T cells; Th1, type 1 helper T cells, Th2 cells, type 2 helper T cells.

Mast cells reside near blood vessels and nerves in tissues throughout the body. They may be activated by a variety of stimuli through various receptors. In the airways, mast cells have receptors for IgE. Once activated, the mast cells produce histamine, leukotrienes, proteases, cytokines, chemokines, and other substances that cause immediate airway inflammation, leading to asthma symptoms. Secreted cytokine and chemokine may contribute to chronic airway inflammation. Mast cells function in innate immunity, host defense against parasites, tissue repair, and angiogenesis.¹⁴

Eosinophils, the least common white blood cells, are often associated with parasite infections, allergic diseases (such as asthma), chronic lung inflammatory states, and hypereosinophilic syndrome. The eosinophil is an important source of major basic proteins, lipid mediators, cytokines, and growth factors, and also secretes mast cell stem cell factor, essential for mast cell growth, activation, chemotaxis, and degranulation.¹⁵

Although the inflammatory cells take center stage, epithelial, endothelial and mesenchymal cells also participate in the inflammatory process.^{2,16}

Cytokines

Cytokines are secreted polypeptides produced by all kinds of cells. They have autocrine, paracrine, or endocrine functions to regulate immunity and inflammation. Binding to specific membrane receptors, cytokines signal the cell via secondary messengers, increasing or decreasing expression of membrane proteins, as well as cell proliferation and secretion. Different cell types can secrete the same cytokine and a given cytokine can act on several cell types (pleiotropy) to stimulate or suppress other cytokines. Cytokines that act as chemotactic agents or chemoattractants for other cells are known as chemokines. Cytokines are redundant, that is, similar functions can be produced by different cytokines that act either synergistically or antagonistically.

Cytokines can be categorized as pro-inflammatory or anti-inflammatory. Major pro-inflammatory cytokines are TNF- α , IL-1 β , IL-6, IL-8, and IFN γ . They activate the immune system and participate in the acute inflammatory response. TNF- α and IL-1 β are the most important pro-inflammatory cytokine and stimulate antigen presentation, adhesion molecule expression on endothelial cells, inflammatory cell activity, and expression of matrix-degrading enzymes, like collagenase. Major anti-inflammatory cytokines include IL-10, TGF- β , and IL-1ra (a natural IL-1 receptor antagonist). Alveolar macrophages secrete the anti-inflammatory cytokines to down regulate the inflammatory response in the lungs.[17,18](#) Receptors for TGF- β are present on virtually all cells. TGF promotes wound healing and scar formation. IL-10 inhibits the production of pro-inflammatory cytokines by T cells, NK cells, and monocytes.[19](#) Increasing evidence indicates that dysregulation of cytokines is an important step in many pulmonary diseases. For example, allergens stimulate Th2 cells. In allergic asthma, APCs activate Th2 cells to produce IL-4 and IL-13, which in turn stimulate B cells to produce IgE and subsequent mast cell degranulation. Activation of Th2 cells also causes IL-5 production, which stimulates eosinophils.[20](#) Mediators released by mast cells and eosinophils produce an asthmatic attack. Many cytokines are associated with COPD, including TNF- α , IFN- γ , IL-1 β , IL-6, and GM-CSF.[21](#) In ARDS, pro-inflammatory cytokines (TNF- α and IL-1 β) are increased [22](#) and the increment of anti-inflammatory cytokines like IL-10 may not keep up with their production. It has been reported that IL-10 is lower in ARDS than in critically ill non-ARDS patients.[23](#) The imbalance of the pro- and anti-inflammatory cytokines may promote the disease.

Acute pulmonary inflammation

Macroscopically, inflammation is characterized by redness, swelling, heat, pain, and loss of function. Microscopically, it is exhibited by vasodilation, increased vascular permeability, and inflammatory cell infiltration. Inflammatory responses are to destroy and remove, as well as to wall off and confine the injurious agents. Furthermore, inflammation stimulates the immune response to promote recovery. Acute lung inflammation is dominated by neutrophils, whereas chronic reactions involve mainly macrophages and lymphocytes. ARDS is an example of acute inflammation not only persisting but also becoming amplified to involve the entire organ. During acute lung insult, endothelial cells are activated to express chemotactic factors, including endothelial-derived adhesion molecules that lead to attachment and diapedesis of leukocytes in the region. A resulting chemotactic gradient first directs neutrophil migration and then further chemokine production to orchestrate formation of granulation tissue comprising cellular matrix, fibroblasts, endothelial cells, and leukocytes.

Bacterial infections

When the lung is exposed to minimal bacterial loads, pathogen clearance operates through innate defenses and the event is generally subclinical. Acute infection results when higher loads of bacteria overcome the local defenses, leading to acute inflammation involving both innate and adaptive defenses. Bacterial colonization results from abnormal innate defenses, establishing an equilibrium between bacterial replication and clearance. Chronic infection occurs when marked a inflammatory response generated by host defense mechanisms fails to clear the bacteria, with continued tissue destruction.[24](#)

When inhaled in a significant load, bacteria overcome primary host defenses by releasing ciliary toxins, pneumolysin, endotoxin, and IgA proteases, thereby disrupting mucociliary clearance.[25](#) Ultimately, bacteria adhere to the epithelium. In response, dendritic cells, alveolar macrophages, and epithelial cells are activated as pathogen markers are identified through toll like receptors (TLRs). Recognition of the pathogen initiates inflammation, which progresses through four phases: initiation, amplification, phagocytosis, and resolution.

Initiation TLRs are membrane-bound pattern-recognition receptors (PRRs). They recognize specific conserved molecular patterns broadly shared by pathogens, known as pathogen-associated molecular patterns (PAMPs). PAMPs are molecules essential for microorganism survival, and innate and adaptive immunity ensue when they are engaged by PRRs.[4](#) There are at least 10 types of TLRs that recognize microbes on the cell surface or in endosomes. TLR-4 recognizes endotoxins and lipopolysaccharide-binding proteins from gram-negative bacteria; TLR-2 recognizes gram-positive bacteria and peptidoglycans.[26](#) In addition, cytosolic PRRs consist mainly of nucleotide oligomerization domain (NOD)-like receptors (NLRs) and function as regulators of innate immune response against microbial pathogens. Stimulation of NOD1 and NOD2, two prototypic NLRs, activates mitogen-activated protein kinases and NF- κ B.[27](#) The NLRs recognize specific components of bacteria and form a cytoplasmic signaling complex with other proteins known as the inflammasome.[28](#) In some cells, inflammasome activation may lead to rapid host cell death (pyroptosis), which may protect the host by preventing bacterial replication.

Amplification After PAMPs are recognized, cell activation increases transcription factors like NF- κ B, producing growth factors, chemokines, adhesion molecules and pro-inflammatory cytokines including IL-8 and TNF- α .[29](#) IL-8 acts as a neutrophil chemotactic agent, and TNF- α increases expression of lung capillary endothelial cell adhesion molecules[30](#) for increased neutrophil adhesion. Activated neutrophils release more IL-8,[31](#) which in turn increases neutrophil recruitment. Also, elastase from activated neutrophils induces epithelial IL-8 production.[32](#) While neutrophils and alveolar macrophages are combating the pathogen in a nonspecific way, dendritic cells present the T lymphocytes with the foreign antigen and cause either a Th1 or Th2 response. The activated T cells and B cells (producing antibodies) follow to defend the body against the bacterial attack. Growth factors and cytokines released from activated T cells further stimulate the macrophages.

Phagocytosis After successfully evading mechanical barriers and ciliary removal, and surviving the actions of surfactants and antibodies, bacteria may encounter complement proteins. Complements facilitate recognition by alveolar macrophages of bacteria through PRRs and prepare bacteria for phagocytosis. At least two additional mechanisms can be activated to enhance killing and clearance of the microbe.[33](#) The first involves alveolar macrophages and their ability to liberate chemotactic factor

that attract nearby neutrophils and initiate inflammatory responses. The second occurs when the bacteria trigger T cells, to release cytokines that stimulate the phagocytic and bactericidal capacity of alveolar macrophages.

Resolution Resolution occurs after a successful host response. Complete bacterial phagocytosis, and killing by reactive oxygen species, bacteriocidal permeability-inducing protein, lactoferrin, elastase, and neutrophil extracellular trap,³⁴ down regulates the host defense system. Resolving lung inflammation depends upon apoptosis as well as timely and adequate removal of acute inflammatory cells by macrophages. During apoptosis, neutrophils and eosinophils undergo surface changes enabling phagocytes to recognize and ingest them. The apoptotic process is modulated through extracellular signaling. For example, neutrophils cultured in the bronchial alveolar lavage fluid from ARDS patient have a longer lifespan than those from patients with normal lungs. Pro-inflammatory cytokines such as GM-CSF may be responsible for apoptosis delay.³⁵ In some circumstances, apoptosis of eosinophils and neutrophils is conversely regulated. For example, dexamethasone enhances apoptosis of eosinophils, but inhibits that of neutrophils, prolonging neutrophil viability.⁵ Resolution of inflammation not only depends on the removal of apoptotic cells but also on suppression of inflammatory mediator production.⁶ Incomplete resolution leads to chronic inflammation.

Viral infections

Viruses activate the innate immune system through cell surface and cytosolic PRRs, which detect viral components (especially nucleic acids). TLR-3 recognizes double-stranded RNA viruses, while TLR-7 and TLR-8 detect single-stranded RNA viruses. The activated immune cells synthesize antiviral type I interferon (IFN), pro-inflammatory cytokines, and chemokines including TNF- α , IL-1 β , IL-6, IL-8, IL-12, and monocyte chemoattractant protein 1.³⁶

Respiratory virus infections elicit primarily a Th1 type response, which is dominated by IFN γ production. Th2 responses are ineffective or even detrimental.³⁷ CD8⁺ cytotoxic T cells as well as NK cells play a key role in viral clearance, although neutralizing antibody is also generated late in a primary infection by influenza and parainfluenza.³⁷ In a secondary infection, both CD4⁺ and CD8⁺ T cells respond promptly. Large populations of memory T cells persist in the airways and lung parenchyma and decrease gradually over several months, and then stabilize at a low level. This progressive loss correlates with a decline in protective cellular immunity, suggesting a critical role of memory T cells in the lung. Viruses are also responsible for episodes of exacerbations of COPD and asthma, where they increase the airway inflammation (acute exacerbation or chronic inflammation).

Parasitic infections

Many protozoa and helminthes involve the respiratory system. Our understanding of the role of TLR in parasitic diseases is just beginning. For example, TLR-2 and TLR-9 are associated with malarial infection,³⁸ whereas TLR-4 involves containment of leishmaniasis.³⁹ Protozoa vary greatly and stimulate distinct immune responses. Protozoa may be phagocytized by macrophages, but many are resistant and may replicate within macrophages.⁴⁰ In resolving *Leishmania* infections, a protective Th1 response by host cells leads to macrophage activation to kill the organism.⁴¹ PRRs are also used to detect molecules on protozoa, which leads to their killing by complement activation and

phagocytosis.[42](#)

Helminthes usually produce Th2 responses, with secretion of IgE and activation of eosinophils, basophils, and mast cells. In contrast, bacteria and viruses typically evoke IFN γ dominant Th1 response with activation of CD8 $^{+}$ cytotoxic T cells, neutrophils, and macrophages. Activated macrophages engulf and destroy microorganisms through expression of inducible nitric oxide synthesis (iNOS). However, in Th2 response to helminthes, macrophage activation is triggered by IL-4, IL-10, IL-13, and IL-21, and does not express iNOS.[43](#) The activated macrophages and eosinophils may contribute to the healing of damaged tissue caused by invasive helminthes. Neutrophils are rapidly recruited in response to invasive helminthes. Eosinophils migrate to the site of infection where they release mediators, help in tissue remodeling, and assist neutrophils to kill the organism.[43](#) IgE is also very important. It forms immune complexes with the organisms that are then eliminated by macrophages.

Chronic pulmonary inflammation

Chronic inflammation occurs when resolution of acute inflammation is incomplete. Chronic inflammatory responses clear necrotic debris and apoptotic cells from acute inflammation; defend against and prevent the spread of persistent infections; and heal and repair the lung tissue damage. The major cells involved are macrophages and lymphocytes. Cytokines are produced by a variety of immune and nonimmune cells. The production of these cytokines can dictate the extent and type of the inflammatory response. In chronic lung inflammation, profibrotic and immunoregulatory Th2 cytokines dominate. Chemokines play a pivotal role in regulating cell trafficking, angiogenesis, and the inflammatory response. They mediate neutrophil infiltration into the lung parenchyma and pleural space by binding to receptors on neutrophils, lymphocytes, monocytes, and dendritic cells.[44,45](#) In mice, inoculation of the airways with *Pseudomonas* leads to persistent release of chemokines and time-dependent neutrophil influx.[46](#) In interstitial pulmonary fibrosis (IPF), chemokine (IL-8) is significantly elevated and correlates with the presence of neutrophils in bronchoalveolar lavage fluid. As mentioned above, apoptosis plays an important role in chronic lung inflammation. During chronic inflammation, abnormal function of inducer or suppressor genes decreases apoptosis of immune cells. This leads to prolongation of inflammatory cell infiltration of the lungs.

Chronic airway inflammation is characteristic in both asthma and COPD, yet there are marked differences in the inflammatory cells involved. Airway eosinophils are prominent in asthma, but not in COPD except during acute exacerbations.[47,48](#) Apoptosis is inversely correlated with the clinical severity of asthma. Asthmatics show more submucosal “nonapoptotic” eosinophils than patients with chronic bronchitis or normal subjects. Bronchial biopsy specimens from asthmatic subjects reveal a higher infiltration of eosinophils expressing anti-apoptotic genes (bcl-2) than those expressing pro-apoptotic oncogenes (p53).[49](#) Decreased T cell apoptosis in asthma may lead to its increased number. CD4 $^{+}$ T cells are more evident in asthma, whereas CD8 $^{+}$ T cells are predominant in COPD.[50](#) Moreover, CD8 $^{+}$ T cells are higher in smokers than asthmatics.[51,52](#) In smokers, the severity of airflow limitation correlates with the number of neutrophils, macrophages, and NK lymphocytes in bronchoalveolar lavage fluid.[51](#) Inflammation in asthma is only in the airways, but in COPD, inflammation extends from the peripheral airways down to the lung parenchyma.

Chronic bronchitis is characterized by airflow obstruction, mucus hypersecretion, and inflammation

throughout the lungs. Neutrophils predominate in the airway lumen, although mononuclear cells, macrophages, CD8⁺ T cells and B cells infiltrate the larger airway walls.⁵³ Plausibly, the severity of airway inflammation can be related to the severity of the disease ⁵¹ and is a better pathologic marker of chronic bronchitis than submucosal gland hypertrophy.

Th2 response is involved in chronic fibroproliferative disorders. Suppression of Th1 response or exaggerated Th2 response can lead to IPF.⁵⁴ Interstitial lung diseases are characterized by proliferative of fibroblasts and production of cytokines, chemokines, and glycosaminoglycans. These cytokines mediate the generation of tissue collagenase, gelatinase, and PGE₂, which augment extracellular collagen and fibrinous matrix degradation. IL-1 α and IL-1 β stimulate production of type I and III collagen from fibroblasts and type IV collagen from epithelial cells. Moreover, production of PGE₂ inhibits fibroblast proliferation.

Th1 primarily involves granulomatous inflammation. Sarcoidosis is the best known of these, although tuberculosis and hypersensitivity pneumonitis are also important.^{55,56} Th2 drives eosinophilic granulomatous diseases, like Churg-Strauss vasculitis.⁵⁷ Although the clinical presentation of these diseases may be different, the inflammatory processes possess a similar propagation of events in the pathogenesis of their development.

Recently, GITR (glucocorticoid-induced TNF receptor-related protein) was found to be important in acute as well as chronic inflammation, and is closely associated with the development of pulmonary fibrosis. Neutrophil infiltration, pro-inflammatory cytokines, and toxic oxygen species are decreased in the pleural fluid in GITR^{-/-} pleurisy mice,⁵⁸ and neutrophils are decreased in the bronchoalveolar lavage fluid of GITR^{-/-} bleomycin-induced pulmonary fibrosis mice. Moreover, lung histology also showed less fibrosis in GITR^{-/-} mice.⁵⁸

Regulation of lung inflammation

The lung provides a huge surface for gas exchange and pathogen contact. While a forceful innate immune response, such as inflammation, is needed to fight off the harmful invaders, effective regulation to suppress the inflammatory processes and limit inflammation-induced damage is also necessary to maintain homeostasis. Such regulatory mechanisms are in place to protect lung function. For example, activation of TLRs may suppress Th1- and Th2- mediated lung inflammation, thus providing negative feedback to prevent excessive lung inflammation.⁵⁹ In addition, cytokines produced by inflammatory cells (IL-10⁶⁰ and TGF- β ⁶¹) can down regulate inflammatory cytokine production and inflammatory response. The lungs provide organ-specific regulatory strategies to prevent excessive inflammation during microbial invasion. For example, Type II epithelial cells in the lung communicate with alveolar macrophages, providing tonic inhibitory effects through TGF- β to limit potential adaptive immune-induced lung inflammation.¹ Recent evidence indicates that neural immune interaction may play an important role in controlling inflammation in a variety of diseases.⁶² Such control involves the peripheral and central nervous systems to regulate the body's reaction. Sensory neurons in the airways may provide a sensing mechanism to detect the inflammatory intensity in the lung for lung-brain communication. Indeed, sensory neurons in the lung are activated during acute lung injury.⁶³ In addition, pro-inflammatory cytokines and mediators, and TLR ligands can stimulate airway sensory neurons,⁶⁴ which may initiate a reflex to suppress production of pro-

inflammatory cytokines.⁶⁵ These negative feedback regulatory mechanisms are important in control of inflammatory intensity. On the other hand, activation of sensory afferents may release neuropeptides, which can induce neurogenic inflammation to intensify the inflammatory response.^{66,67}

Concluding remarks

Inflammation is an important feature of many pulmonary diseases such as pneumonia, ARDS, asthma and COPD. Varied and disparate strategies have been adopted to intervene in pulmonary immune responses. In addition to looking at the cytokines, cytokine receptors, and cell-surface molecules, cellular signal transduction and gene activation have been targeted for therapy. It is apparent that to understand the mechanism of upcoming future modalities of treatment, the physician should have a basic understanding of the underlying cellular mechanisms of inflammation.

Table 1

Mechanisms in different types of infection

	Response	Examples	
Viruses	<p>PRRs recognize PAMPs → NF-κB activation → ↑synthesis of antiviral type 1 IFNs (α, β) and inflammatory cytokines (TNF-α, MCP1, IL-6, 8, 12)36</p> <p>Primary infection:</p> <p>CD8+ T cells clearing up the infection37</p> <p>Secondary infection:</p> <ol style="list-style-type: none"> 1. Recruitment of circulating memory T cells (CD8+, CD4+) (antigen nonspecific; IFN-γ mechanism) 2. Antigen-specific T cells produced by proliferation of quiescent central memory T cells (CD8+) in BALT68 	<p>ssRNA viruses:</p> <ol style="list-style-type: none"> 1. Influenza A: 2. RSV: <p>dsDNA viruses</p> <ol style="list-style-type: none"> 1. Adenovirus: 2. HSV: 	<p>TLR369 and TLR770</p> <p>TLR471</p> <p>CDS72 → IFN, IL-6, TNF-α synthesis</p> <p>TLR2,73 TLR974</p>
Bacteria	<p>PRRs (TLR2 for Gm+ peptidoglycan; TLR4 for Gm-LPS) on APCs recognize PAMPs → NF-κB activation → TNF-α, IL-1, 8,24 → neutrophil chemotaxis → phagocytosis → resolution</p>	<p><i>Staphylococcus aureus</i></p> <p><i>Pseudomonas aeruginosa</i></p> <p><i>Streptococcus pneumoniae</i></p> <p><i>Klebsiella pneumoniae</i></p> <p>Mycobacteria</p>	<p>TLR275</p> <p>TLR5 recognizes Flagellin76 Alveolar macrophages (TLR2 less important)77</p> <p>TLR4 → CD4+ T cells → IL-17 → epithelial cells→ chemokines78,79</p> <p>TLR2, 480 → cytotoxic CD8+ T cell activation and IFN-γ production.81</p>
Parasites	<p>Three mechanisms involve the respiratory system:82 stimulation of hypersensitivity during life cycle direct parenchymal or pleural invasion migration from infected organs</p> <p>Parasite specific-IgE form immune complexes which are removed by macrophages82 Protozoa vary in structure and biochemistry → distinct immune responses. Helminths → Th2 response and alternate macrophage activation83 Major:</p>	<ol style="list-style-type: none"> 1. Protozoa: <ul style="list-style-type: none"> Leishmania Plasmodium 2. Helminths: <ul style="list-style-type: none"> Schistosoma 	<p>TLR484</p> <p>TLR2, 938 → NK cells, NKT cells to produce IFN-γ85</p> <p>Parasite eggs→ granulomatous response via TLR 2,382</p>

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Abbreviations: APCs, antigen presenting cells; BALT, bronchial-associated lymphoid tissues; dsDNA, double-stranded DNA; HSV, herpes simplex virus; IFN, interferon; MCP1, monocyte chemoattractant protein 1; NK cells, natural killer cells; PAMPs, pathogen-associated molecular patterns; PRRs, pattern recognition receptors;

RSV, respiratory syncytial virus; ssRNA, single-stranded RNA; TLR, Toll-like receptors.

Table 2

Pathology and immune mechanisms in some common respiratory diseases

	Pathophysiology	Pathology	Cells	Mediators
Acute				
Pneumonia	Parenchymal inflammation	Viral, bacterial, parasitic	APC, 34	IL-8, TNF-
	Lobar/patchy consolidation	Invasion→recognition→Inflammatory amplification→phagocytosis→resolution	neutrophil, eosinophil (parasites) Macrophage (mycobacteria) Th1/Th2 response	α , NETs 4 IL-1 β
ARDS/ALI	PaO ₂ /FiO ₂ ≤ 200 (≤300 ALI)	Sepsis, trauma, aspiration	Neutrophil 86	Lipid
	PCWP ≤18 mmHg	Early phase: ↑capillary permeability alveolar edema and necrosis ↓surfactant: alveolar collapse	Macrophage 87 Type I and II Pneumocytes 88	mediators, Proteases, NF- κ B,
	Bilateral infiltrates	Late phase: fibrosis	Fibroblast, Endothelial cell	Growth factors 89 IL-1 β , TNF- α 90
Chronic				
COPD	↑TLC, RV, ↓VC, FEV ₁ /FVC	Alveolar apoptosis 91	Macrophage	MMP12, 8,
	↓DLCO	Poor phagocytosis of apoptotic neutrophils→necrosis→↑NE release ↓VEGF: 92 Chronic parenchymal and airway inflammation	Neutrophil CD8+ T cell Airway epithelial cell	9, cathepsin S,L,G 93 NE, IFN- γ , MIG 94 TGF- β , EGF, PDGF 95
Asthma	↑FEV ₁ > 12%/200 ml after BD	Airway inflammation 96	Eosinophil, 97	↓ IL-10, 102
	↓FEV ₁ /FVC	Fibrosis and SMC hyperplasia ↓ tolerogenic immune response	Mast Cell, Neutrophil 98 Macrophage, DC, Airway SMC Epithelial cell, Fibroblast 99 CD4+ T cells, 100 Basophil 101	TGF- β 103 ↑IL-17 104 and IL-4, 5, 9, 13 15

	Pathophysiology	Pathology	Cells	Mediators
IPF	↓FEV ₁ , FVC,	Epithelial→mesenchymal transition ¹⁰⁵	Fibroblast	IL-8, TNF-
	TLC, RV, DLCO	Injury→mediator release: fibrosis ¹⁰⁶	Airway	α, TGF-
	↔FEV ₁ /FVC	↑angiogenesis	epithelial cell	β ^{108,109}
		Damaged basement membrane ¹⁰⁷	Type II pneumocyte ¹⁰⁷	IL-4, 5, 13 ^{110,111}

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Abbreviations: ALI, Acute lung injury; APC, antigen presenting cells; ARDS, Acute respiratory distress syndrome; BD, Bronchodilator; COPD, Chronic obstructive pulmonary disease; DC, Dendritic cell; DLCO, Diffusing capacity of lung for Carbon monoxide; EGF, Endothelial growth factor; FEV₁, Forced expiratory volume in 1 sec; FiO₂, Fraction of inspired oxygen; FVC, Forced vital capacity; IFN-γ, Interferon gamma; IL, Interleukin; MIG, Monokine induced by gamma interferon; MMP, Matrix metalloproteinases; NE, Neutrophil elastase; NETs, Neutrophil extracellular traps; NF-κβ, Nuclear factor kappa beta; PaO₂, Partial pressure of arterial oxygen; PCWP, Pulmonary capillary wedge pressure; PDGF, Platelet derived growth factor; RV, Residual volume; SMC, Smooth muscle cell; TGF-β, Transforming growth factor beta; TLC, Total lung capacity; TNF-α, Tumor necrosis factor alpha; Treg, Regulatory T cell; VC, Vital capacity; VEGF, Vascular endothelial growth factor.

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