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Host Recovery from Respiratory Viral Infection

Xiaoqin Wei,[1,2,*] Harish Narasimhan,[1,3,*] Bibo Zhu,[1,2,*] and Jie Sun[1,2,3]

[1]Carter Immunology Center, University of Virginia, Charlottesville, Virginia, USA; email: js6re@virginia.edu

[2]Division of Infectious Disease and International Health, Department of Medicine, University of Virginia, Charlottesville, Virginia, USA

[3]Department of Microbiology, Immunology and Cancer Biology, University of Virginia, Charlottesville, Virginia, USA

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*These authors contributed equally to this article

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Abstract

Emerging and re-emerging respiratory viral infections pose a tremendous threat to human society, as exemplified by the ongoing COVID-19 pandemic. Upon viral invasion of the respiratory tract, the host initiates coordinated innate and adaptive immune responses to defend against the virus and to promote repair of the damaged tissue. However, dysregulated host immunity can also cause acute morbidity, hamper lung regeneration, and/or lead to chronic tissue sequelae. Here, we review our current knowledge of the immune mechanisms regulating antiviral protection, host pathogenesis, inflammation resolution, and lung regeneration following respiratory viral infections, mainly using influenza virus and SARS-CoV-2 infections as examples. We hope that this review sheds light on future research directions to elucidate the cellular and molecular cross talk regulating host recovery and to pave the way to the development of pro-repair therapeutics to augment lung regeneration following viral injury.

INTRODUCTION

Respiratory viral infections with epidemic and pandemic potential pose an omnipresent threat to public health. Influenza virus is the causative agent of annual influenza epidemics and has led to four pandemics since 1918. The ongoing COVID-19 pandemic caused by SARS-CoV-2 infection has resulted in catastrophic loss of human lives, with severe disruption of healthcare and socioeconomic systems worldwide. As SARS-CoV-2 and influenza viruses continue to evolve, there is significant concern about new pathogenic variants capable of escaping vaccine- or infection-induced preexisting immunity.

Clinical manifestations of respiratory viral infections range from asymptomatic to severe acute illness and even death. The most common symptoms include fatigue, runny nose, fever, cough, tracheobronchitis, and pharyngitis. In severe cases, patients may develop bronchiolitis, pneumonia, and acute respiratory distress syndrome (ARDS). As highlighted by the COVID-19 pandemic, respiratory viral infections may also result in extrapulmonary disease including cardiac complications (1, 2). Besides acute morbidity, there is growing evidence that a considerable proportion of people who recover from respiratory viral infections, including COVID-19, may harbor long-term symptoms and diseases (chronic sequelae) in the respiratory tract or systemically. Age, pregnancy, and comorbidities including obesity and cardiopulmonary disorders are known risk factors for adverse outcomes following respiratory viral infections (3).

Respiratory viruses mainly target and productively replicate in cells lining the airways and alveolar space to cause lung injury, while also triggering innate and adaptive antiviral host responses. After viral clearance, various immune and nonimmune cells are actively involved in resolving inflammation and repairing the damaged lung tissue. Dysregulated (delayed, exaggerated, or prolonged) host responses often contribute to, if not drive, severe acute host morbidity, and they also lead to dysfunctional repair and subsequent chronic sequelae (**Figure 1**). In the following sections, we discuss protective host antiviral responses, pathogenesis, inflammation resolution, lung repair, and chronic sequelae after respiratory viral infection, mainly using influenza virus and SARS-CoV-2 as models.

HOST ANTIVIRAL RESPONSES

Upon encountering a respiratory virus, the host initiates a cascade of events to defend itself and clear the pathogen (4). Nearly all cell types within the lung, structural cells and immune cells, have the ability to detect and respond to viral infections via the coordinated activity of cell-intrinsic, innate, and adaptive immune responses (**Figure 2**).

Cell-Intrinsic Antiviral Responses by Nonimmune Cells

The various nonimmune structural cells of the lung, including epithelial, endothelial, and mesenchymal cells, support physiological pulmonary function, but they also are at the front line of viral invasion. Influenza virus and SARS-CoV-2 primarily target airway and alveolar epithelial cells upon successfully overcoming the mucous barriers and mucociliary clearance within the airways. From there, the virus can spread to both immune and nonimmune cells (5, 6). During this process, viruses are detected by ubiquitously expressed pattern recognition receptors, which recognize conserved viral pathogen-associated molecular patterns (7). Viral double-stranded RNA intermediates are detected by cytoplasmic retinoic acid–inducible gene I (RIG-I)-like receptors (RLRs), including RIG-I and MDA5, which interact with the adaptor protein MAVS, to induce production of type I interferon (IFN-I), IFN-III, and proinflammatory cytokines to further activate downstream pathways and establish an antiviral state (8). The cytoplasmic DNA sensor cGAS was also reported to respond to RNA viruses and activate STING-dependent downstream

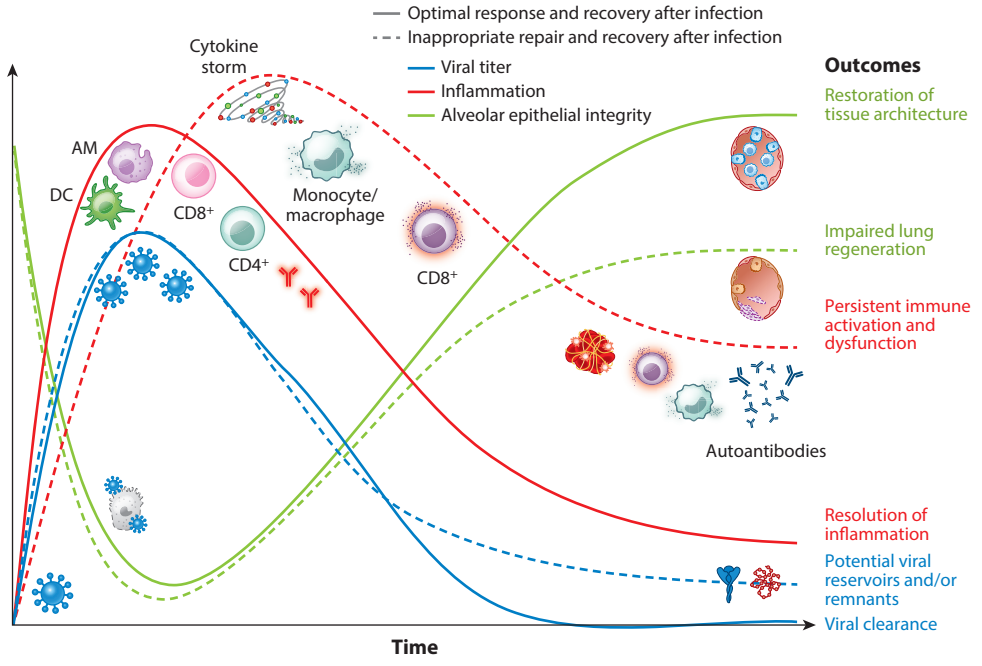

Figure 1

An overview of the pulmonary milieu during an acute respiratory viral infection. Appropriate immune processes (*solid red curve*) resulting in effective viral clearance (*solid blue curve*) due to coordinated innate and adaptive responses. Resolution of inflammation facilitates regeneration of the damaged tissue, restoring tissue architecture (*solid green curve*) of the lung and reestablishing physiological pulmonary function. Dysregulation of this cross talk results in delayed and exuberant inflammatory responses (*dashed red curve*), inducing collateral immunopathology while potentially failing to fully clear virus and resulting in persistent viral reservoirs and/or remnants (*dotted blue curve*). Sustained inflammation also inhibits reparative processes (*dotted green curve*), potentially leading to chronic pulmonary disease. Abbreviations: AM, alveolar macrophage; DC, dendritic cell.

antiviral pathways for the production of interferons (9). Moreover, cytoplasmic sensors ZBP1 and NLRP3 orchestrate virus-induced programmed cell death and inflammasome activation, limiting viral infection (8). Toll-like receptors (TLRs) are transmembrane receptors located in the plasma or endosomal membrane, among which TLR3, 7, and 8 recognize viral RNA and activate antiviral signaling pathways (8). In addition to epithelial cells, endothelial cell activation alters vascular permeability and contributes to the circulation of inflammatory factors, facilitating the influx of immune cells to the site of infection. Airway mesenchymal cells, including fibroblasts, smooth muscle cells, pericytes, and other stromal cells, further produce growth factors, cytokines, and chemokines to regulate immune cell migration and function during viral infection (3). Thus cell-intrinsic responses mediated by structural cells of the lung set up the cellular landscape for subsequent antiviral activities by innate and adaptive immune cells.

Innate Immune Cells

Alveolar macrophages (AMs) patrol the alveolar space, maintaining close contact with the alveolar epithelial layer, to phagocytose local cellular debris, invading particles, and pathogens. During homeostasis, AMs are the primary immune population in both mouse and human lungs and typically mediate anti-inflammatory functions. However, upon infection of the alveolar epithelium,

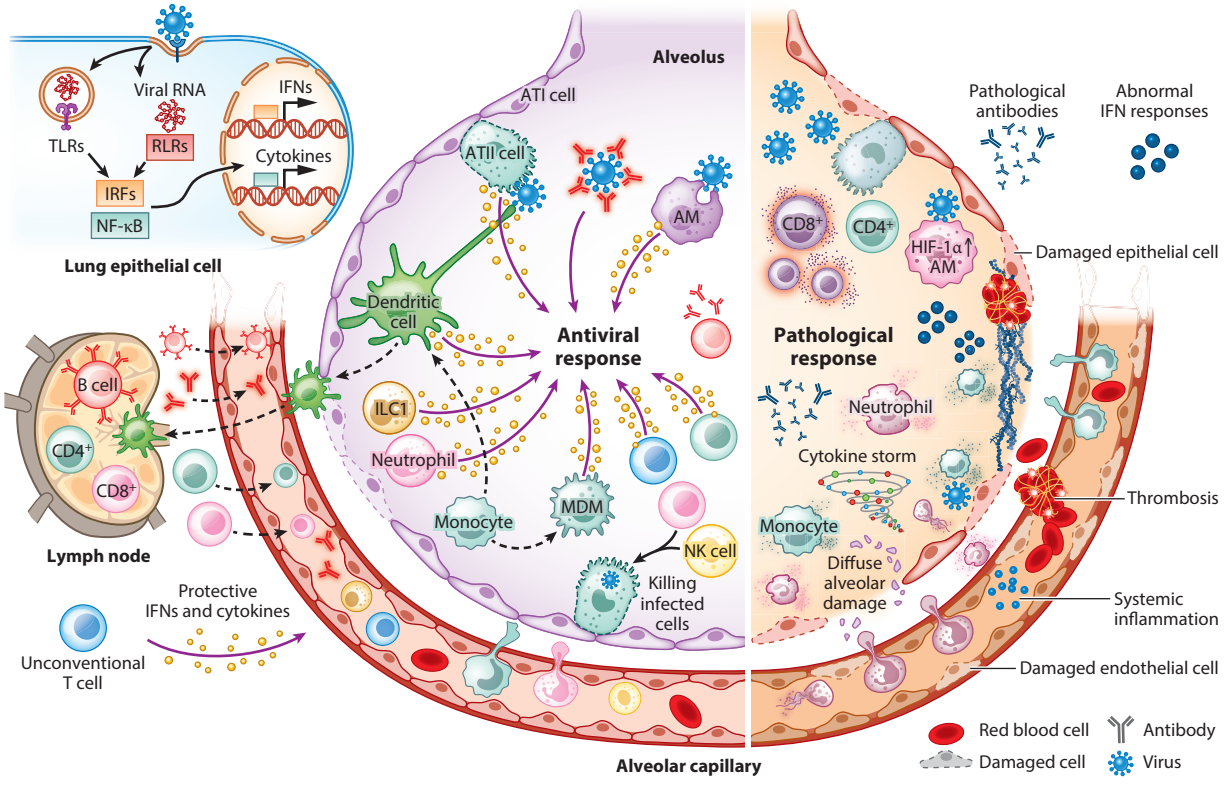

Figure 2

Host antiviral and pathological responses during respiratory viral infection. Respiratory viruses enter the host via the respiratory epithelium. Epithelial cells play key roles in initiating host responses by detecting the virus via pattern recognition receptors, leading to activation of antiviral interferon signaling and secretion of proinflammatory cytokines and chemokines. Alveolar macrophages recognize and phagocytose viruses to further activate antiviral and inflammatory responses. The initial inflammation attracts and activates monocytes, monocyte-derived macrophages, dendritic cells, NK cells, neutrophils, and innate lymphoid cells to the lungs, where they contribute to the elimination of the infected cells. Dendritic cells recognize viral antigens and migrate to the draining lymph nodes to activate T cells. Antiviral T cell responses are mediated by $CD4^+$ T helper cells and $CD8^+$ cytotoxic T cells. $CD4^+$ T cells coordinate B cell responses to produce antibodies and neutralize the virus. Alternatively, excessive immune responses in the lungs can result in accumulation of inflammatory immune cells, including HIF-1α-expressing alveolar macrophages, monocytes, neutrophils, $CD4^+$ T cells, and hyperactivated $CD8^+$ T cells. These events trigger a dysregulated interferon response and overproduction of proinflammatory cytokines, resulting in diffuse alveolar damage, a systemic inflammatory state, and thrombosis, further contributing to tissue damage and host mortality. In addition, the afucosylated antibodies and autoantibodies are associated with severe disease outcomes. Abbreviations: AM, alveolar macrophage; ATI, alveolar epithelial type I; IFN, interferon; ILC1, type 1 innate lymphoid cell; MDM, monocyte-derived macrophage; NK, natural killer; RLR, RIG-I-like receptor; TLR, Toll-like receptor.

AMs are among the first immune cells to encounter virus and initiate a plethora of antiviral and inflammatory responses (10, 11), as evidenced by the substantial production of interferons (12, 13). In addition to secreting potent antiviral molecules, AMs phagocytose antibody-opsonized influenza virus particles via the Fc receptor, thereby preventing viral dissemination to neighboring alveolar epithelial cells (14). Notably, AMs were found to harbor SARS-CoV-2 RNA (15), potentially due to direct viral infection or phagocytosis of virus and/or infected cells. However, for reasons still under investigation, SARS-CoV-2 infection of AMs triggers minimal

IFN-I production compared to influenza virus infection, potentially contributing to the delayed interferon production observed in COVID-19 (16, 17).

Interstitial macrophages are another lung-resident macrophage population that likely participates in antiviral immunity following infection (18); however, their precise functions and significance to host responses remain to be elucidated. Circulating monocytes respond to virus-induced inflammatory signals and infiltrate infected tissues, contributing to antiviral immunity, but they may also cause bystander inflammation, potentially damaging host tissue. Upon activation, monocytes produce IFN-I, which provides essential signals to further activate other cell types, including NK cells and $CD8^+$ T cells (19). Consistent with this, impaired monocyte recruitment in CCR2-deficient mice resulted in diminished priming of influenza virus–specific $CD8^+$ T cell responses and delayed viral clearance (20, 21). Notably, SARS-CoV-2 can nonproductively infect human monocytes via antibody-mediated opsonization (22). Further mechanistic studies are required to determine whether monocytes participate in protective antiviral immunity against SARS-CoV-2 infection.

Dendritic cells (DCs) play a crucial role in antiviral immunity by forming a bridge between the innate and the adaptive immune systems. This communication is mediated by three major subsets of DCs: conventional type 1 DCs (cDC1s), cDC2s, and plasmacytoid DCs (pDCs). cDC1s are present mainly in the mucosa and vessel walls in the lungs, whereas cDC2s reside in the lamina propria of the lung (23). Upon viral invasion, both cDC1s and cDC2s can migrate to the draining lymph nodes to activate T cells, but cDC1s preferentially prime $CD8^+$ T cells while cDC2s more efficiently activate $CD4^+$ T cells following influenza infection (24). In people with severe COVID-19, cDCs were drastically depleted from the blood, suggesting an impairment or delay in the activation of virus-specific T cells (25). Older host age further diminishes DC migration and T cell priming following both influenza virus and SARS-CoV-2 infection via a mechanism dependent on prostaglandin D_2 (26, 27). In contrast to cDCs, which exert their functions primarily via T cells, pDCs directly produce enormous amounts of IFN-I to establish an antiviral state; however, their importance during respiratory viral infections is context dependent. While pDCs are the major source of IFN-I upon respiratory syncytial virus (RSV) infection, they are dispensable for IFN-I production and antiviral immunity following influenza infection (28, 29). Notably, the frequency and function of pDCs in the blood of patients with severe COVID-19 are diminished (30), which potentially contributes to suboptimal IFN-I production during the early phase of SARS-CoV-2 infection.

NK cells belong to the family of innate lymphoid cells (ILCs) and perform crucial roles during early antiviral responses, including killing infected cells and producing effector cytokines. Both receptors for innate cytokines that are generated after infection and receptors for ligands on target cells can induce NK cell cytotoxicity and cytokine production. Given their essential roles in viral clearance, depletion and dysfunction of NKs are associated with increased susceptibility to respiratory viral infections, including SARS-CoV-2 (31, 32). Type 1 ILCs (ILC1s) are the innate counterparts of IFN-γ-producing T helper 1 (Th1) cells, which also contribute to limiting viral infection and dissemination (33).

Adaptive Immune Responses

Innate immune responses are the front line controlling viral replication and dissemination; however, complete clearance of infectious virus typically requires the adaptive arm of the immune system. Adaptive immunity encompasses the coordinated activity of $CD4^+$ Th cells, $CD8^+$ cytotoxic T lymphocytes (CTLs), and B cells (cellular immunity) as well as pathogen-specific antibodies (humoral immunity) triggered during acute disease. Moreover, the adaptive system

confers long-term immunity by maintaining long-lived plasma cells and memory lymphocytes, which are poised for activation and expansion upon subsequent infection.

Cellular antiviral responses are initiated when naive virus-specific T cells are activated by antigen-presenting cells (mainly cDCs) in the lung draining lymph nodes. Activated T cells undergo expansion and eventually differentiate into effector T cells. Following influenza infection, $CD4^+$ T cells predominantly facilitate the activation and differentiation of antibody-producing B cells and support $CD8^+$ T cell responses (34), whereas some $CD4^+$ T cell populations also exhibit perforin-mediated cytolytic activity (35, 36). $CD8^+$ T cells recognize and eliminate virus-infected cells via perforin and granzyme-mediated cytolytic mechanisms or death receptor–mediated apoptosis. Additionally, virus-specific CTLs are potent producers of proinflammatory mediators such as IFN-γ and TNF (tumor necrosis factor), as well as anti-inflammatory IL-10, thus maintaining the balance between efficient antiviral responses and immunopathology (37, 38). Following viral clearance, most effector T cells undergo apoptosis during the contraction phase, except for a group of antigen-specific T cells that eventually become circulating and tissue-resident memory T (Trm) cells, providing long-term cellular immunity against reinfection (39).

Consistent with the protective role of T cells during viral infections, the magnitude of T cell responses inversely correlated with host disease severity following SARS-CoV-2 infection (40, 41). However, virus-specific T cell immunity is compromised in COVID-19 patients more than 65 years old, potentially explaining the elevated risk of severe disease in the elderly (42, 43). Of note, both SARS-CoV-2 infection and vaccination induce the formation of systemic antigen-specific memory T cells, whereas only infection generates S-specific Trm cells in the respiratory tract (44–46). Since it is well established that pulmonary Trm cells facilitate rapid responses in situ and provide superior protection against respiratory viral infections (47), vaccination platforms inducing strong local pulmonary Trm cell responses may be a useful strategy for effective protection against influenza virus, SARS-CoV-2, and emerging variants of concern (46, 48).

The primary contribution of B cells to antiviral immunity is through the production of virus-specific antibodies. A distinct subset of $CD4^+$ T cells termed follicular helper T (Tfh) cells are required for optimal activation and differentiation of B cells during infection to produce neutralizing and non-neutralizing antibodies (49). Neutralizing antibodies bind to important surface structures on free viral particles and prevent productive infection of susceptible cells, thereby controlling viral dissemination. As observed during influenza virus infection, effective humoral responses involve the induction of virus-specific neutralizing antibodies targeting surface glycoproteins—hemagglutinin and neuraminidase—to block infection (50). Following SARS-CoV-2 infection, neutralizing antibodies typically target the receptor-binding domain of the S glycoprotein and block interactions with the ACE2 receptor (51). However, SARS-CoV-2 variants of concern, including omicron, harbor extensive mutations within the receptor-binding domain and thus significantly evade humoral immunity generated following natural infection or vaccination (52, 53). Antibody responses following influenza infection are also predominantly strain specific (54). However, antibodies directed against the conserved stalk region of the influenza virus hemagglutinin protein provide broad protection against different influenza virus strains, which is the goal of the universal influenza vaccine (55). In addition to neutralizing antibodies, non-neutralizing, virus-specific antibodies bind to the virus without affecting its infectivity, instead triggering antibody-dependent phagocytosis and cytotoxicity to clear virus or virus-infected cells (50, 56).

Unconventional T cells are a family of cells endowed with both innate and adaptive immune properties and are classified into three main classes: mucosal-associated invariant T (MAIT), γδ T, and natural killer T (NKT) cells. Unlike traditional $CD4^+$ and $CD8^+$ T cell subsets, these cells recognize nonpeptide antigens and have emerged as important players in mucosal immunity

(57). Upon activation, unconventional T cells can rapidly respond to viral infection by producing diverse cytokines without the need for clonal expansion or differentiation (57). In addition to promoting antiviral responses and viral clearance via cytokines, unconventional T cells also exhibit cytolytic activities, killing virus-infected cells following influenza virus infection (58–60). Interestingly, several studies consistently report a profound decline in circulating MAIT (61), γδ T (62), and NKT cells (62, 63) during severe COVID-19, with a concomitant enrichment in the airways. Moreover, these cells exhibit a strongly activated phenotype characterized by a functional bias toward IL-17 production (61, 62). Since most reports investigating the role of unconventional T cells in COVID-19 are based on peripheral blood samples, their precise contribution to local antiviral immunity within the lung remains unknown.

PATHOLOGICAL HOST RESPONSES

Severe disease following respiratory viral infections is associated with destruction of the lung architecture, due to a combination of virus-induced cytopathic effects and uncontrolled host immune responses (**Figure 2**). The loss of structural cells of the lung, including epithelial, endothelial, and mesenchymal cells, compromises gas exchange, resulting in impaired pulmonary function as well as bronchiolitis, pneumonia, and ARDS. Severity and poor outcomes of influenza, SARS, MERS (Middle East respiratory syndrome), and COVID-19 are typically attributed to exuberant immune responses, rather than elevated viral loads (64–67). Thus, the crucial challenge for the host during acute disease is to balance antiviral responses to efficiently clear virus without significantly compromising tissue architecture and function. In this section, we summarize major immune-mediated pathological mechanisms underlying adverse outcomes during respiratory viral infections.

Dysregulation of Soluble Factors

Chemokine and cytokine responses are essential for orchestrating protective responses against viral infection. However, strict regulation of these highly potent molecules is required to prevent morbidity and mortality. As discussed above, IFN-I and IFN-III are essential antiviral cytokines; however, delayed and/or excessive induction of interferons triggers a cascade of events resulting in uncontrolled inflammation and impaired lung recovery. Consistent with this notion, IFN-I receptor deficiency in certain genetic backgrounds decreases morbidity and lung pathology following influenza virus and SARS-CoV-1 infections (68, 69). Interestingly, interferon responses are context dependent in COVID-19, evidenced by their protective role in the upper respiratory tract, whereas elevated levels of IFN-I and IFN-III in the lower respiratory tract are associated with severe disease, characterized by a damaged epithelial barrier and potential susceptibility to secondary bacterial superinfections (70, 71). Therefore, the location, magnitude, timing, and duration are key determinants of the protective or pathological roles of interferons in respiratory viral infections.

Besides interferons, elevated levels of a variety of proinflammatory factors such as IL-6, TNF, and CCL2, often referred as cytokine storm, are a consistent observation during severe disease in patients with different respiratory viral infections and often result in a systemic inflammatory state and multi-organ dysfunction (72). Furthermore, cytokine-mediated endothelial activation, dysfunction, and cell death may contribute to systemic coagulation and thrombosis—a phenomenon termed thromboinflammation (73)—a prominent feature of COVID-19. Therefore, blocking cytokine release and/or downstream signaling may hold great promise for treating severe respiratory viral infections. Thus far, however, the therapeutic efficacy of inhibiting inflammatory cytokines in this context remains limited in both animal models and clinical settings (74, 75). In addition to

cytokines and chemokines, excessive and sustained complement activation has also been implicated in the pathogenesis of respiratory viral infections. High circulating levels of C5a-C5aR1, sC5b-9, and C4d were observed in patients with severe COVID-19 (76). Moreover, complement activation is known to trigger the coagulation cascade and is considered a driver of COVID-19-associated thromboinflammation (76). Therefore, interventions targeting the overactive complement system may dampen severe disease during respiratory viral infection (77–79).

Innate Immune Cell–Mediated Pathogenesis

As previously mentioned, AMs are likely among the first immune cells to encounter respiratory viruses. Upon viral recognition, AMs switch from an anti-inflammatory state to initiate antiviral and inflammatory responses by producing numerous proinflammatory mediators (10, 11). However, dysregulated AM responses also contribute to viral pathogenesis, with exaggerated Wnt-β-catenin signaling known to promote severe pulmonary inflammation and pathology following influenza virus and SARS-CoV-2 infection (80, 81). Moreover, the accumulation of other myeloid cells, including $CCR2^+$ inflammatory monocytes and monocyte-derived macrophages or DCs, in the respiratory tract is a hallmark of severe respiratory viral infection (82). Monocytes activated via detection of virus, direct viral infection, or cytokines secrete large amounts of inflammatory cytokines and are known to drive excessive pulmonary inflammation following influenza virus and SARS-CoV-1 infections (83). Aberrant circulating and pulmonary monocyte activity has also been implicated in severe COVID-19, suggesting a conserved pathological role in respiratory viral infections (25, 84). Notably, monocytes can be directly infected by SARS-CoV-2, at least in part via antibody-dependent enhancement, triggering inflammasome activation, systemic inflammation, and pathology (22, 85). In light of these findings, researchers are actively pursuing the strategy of inhibiting monocyte infiltration and resultant inflammation as a therapy for severe COVID-19 and other respiratory viral infections.

As one of the first responders to migrate to the lung during infection, neutrophils may facilitate the clearance of virus and virus-infected cells. As observed with other innate cells described above, clinical studies suggest a potential detrimental role for excessive neutrophilic inflammation in severe respiratory viral infections (86). Adverse outcomes following influenza virus and SARS-CoV-2 infections have been associated with increased neutrophil numbers, neutrophil extracellular trap (NET) formation, and neutrophil activation (87–89). Maladaptive neutrophil responses and NET formation likely propagate pulmonary inflammation, resulting in damage of the airway and alveolar epithelium, compromised lung function, and microvascular thrombosis (90, 91). Consistent with clinical findings, partial depletion of neutrophils alleviates pulmonary inflammation and host morbidity following influenza virus infection (92). Although the mechanisms underlying the pathological activity of neutrophils following viral infections are still unclear, targeting exuberant neutrophilic responses remains a viable therapeutic avenue to mitigate severe disease.

Recent studies have highlighted the dysregulation of additional innate immune cells in severe disease following respiratory viral infections. $CD1c^+$ cDCs are enriched within the lungs of patients with severe COVID-19, where there is a concomitant loss of $CD123^{high}$ pDCs, a phenomenon associated with development of ARDS (25). Mast cell degranulation enhanced inflammation within the alveolar epithelium, promoting lung injury following influenza virus and SARS-CoV-2 infections (93, 94). Increased production of cytokines such as IFN-γ by ILC1s and NK cells has also been associated with severe COVID-19 (88). As high-dimensional techniques such as spectral flow cytometry, single-cell RNA sequencing, and multi-omics are adopted more frequently to study patient samples, we will likely identify an even larger number of cell types and potentially specific subsets implicated in the development of severe disease following respiratory viral infections.

Adaptive Immune System–Mediated Pathogenesis

Timely and robust induction of adaptive T and B cell responses is vital for antiviral responses and development of long-term immunity to subsequent infections. However, dysregulation in the form of aberrant, delayed, or excessive adaptive responses may induce widespread immunopathology, resulting in increased morbidity and mortality. During acute infection, T cells secrete numerous proinflammatory cytokines, including TNF-α and IFN-γ, contributing to pulmonary inflammation typically aimed at viral clearance (38, 95). However, several T cell subsets and associated cytokines contribute to lung pathology and poor outcomes, evidenced by the enrichment of $CXCR3^+CD8^+$ T cells during influenza infection (96) and virus-specific overactivated $CD4^+$ T cells in COVID-19 (41, 97). Moreover, pathogenic Th1 and Th17 cells with high expression of GM-CSF are associated with increased pulmonary inflammation (84, 98). Excessively activated $CD8^+$ T cells, marked by high expression of activation markers, cytotoxic molecules, and/or complement receptors, are also implicated in the development of severe COVID-19 (44, 84, 99). Indeed, immune complex–mediated degranulation of $CD16^+CD8^+$ T cells induces endothelial cell injury, likely contributing to endotheliitis within the lung and thromboinflammation (100). As several reports have now confirmed a pathological role for dysregulated T cell responses, it is crucial to dissect the molecular mechanisms dictating protective versus detrimental functions following respiratory viral infections.

Aberrant B cell and antibody responses have also been reported in severe respiratory viral infections. IL-10-producing regulatory B lymphocytes that suppress Th1 cell responses are biomarkers of lung disease severity in RSV-infected infants (101). Impaired germinal center formation has been observed in COVID-19 patients, and this might skew humoral responses toward an extrafollicular class-switched B cell response, potentially promoting proinflammatory responses (102, 103). The induction of atypical afucosylated virus-specific IgGs during COVID-19 may also contribute to excessive local and systemic inflammation (81, 104, 105). This effect is likely due to the enhanced binding capacity of afucosylated antibodies to Fc receptors on monocytes and macrophages, which promotes antibody-dependent viral entry to induce inflammatory cell death, systemic inflammation, platelet activation, and thrombosis (81). Furthermore, autoantibodies have now emerged as a consistent feature of severe COVID-19 outcomes, where a high proportion of antibodies target IFN-I, contributing to delayed viral clearance, lymphopenia, and tissue damage (6). Additional studies are required to elucidate the mechanisms responsible for the induction as well as subsequent effects of pathological antibodies during SARS-CoV-2 infection.

RESOLUTION OF INFLAMMATION AND IMMUNE-MEDIATED REPAIR

Reestablishing physiological pulmonary function after viral infection requires not only rapid elimination of the virus but also resolution of inflammation and restoration of the lung architecture damaged during acute disease. This process of resolution and repair is facilitated by a complex interplay of signaling pathways and mediators involving diverse immune and structural cells of the lung.

Macrophages

Following viral clearance, AMs clear lung debris and apoptotic cells, which is essential to eliminate inflammatory triggers and promote resolution of inflammation. In this phase, epithelial cells express CD200 and TGF-β that can bind to cognate receptors expressed on AMs, inhibiting AM inflammation and instead activating their anti-inflammatory and repair programs (106). Consistent with this, the expression of CD200R is diminished in patients with severe COVID-19, further indicating a regulatory role for CD200-CD200R signaling in resolution

of inflammation (107). The transcription factor PPAR-γ, known to regulate AM development and maintenance, is required for the pro-repair activity of AMs (108). In concordance with this, myeloid PPAR-γ deficiency leads to impaired tissue recovery and the development of chronic fibrotic sequelae following influenza virus infection (20, 108, 109). Other transcription factors such as β-catenin and HIF-1α also modulate the inflammatory and reparative roles of AMs following infection, as evidenced by accelerated resolution of inflammation and lung repair upon their deletion in AMs (80).

Viral infections typically result in a partial depletion of the resident AMs around the peak of inflammation, requiring subsequent reconstitution of the AM pool via AM proliferation and/or replenishment through monocyte differentiation (80, 110, 111). To this end, β-catenin^{low}HIF-1α^{low} AMs with the capacity for self-renewal serve as progenitors for the wound-healing AM population, promoting tissue repair processes by secreting numerous epithelial and endothelial growth factors (80). Adverse outcomes in patients with severe COVID-19 exhibiting a sustained loss in resident AMs despite the accumulation of monocyte-derived macrophages further reiterate the essential regulatory and pro-recovery roles of AMs (99, 112, 113). In addition to AMs, a recently identified interstitial macrophage subset, nerve- and airway-associated macrophages, was found to exhibit an alternative activation phenotype and exerted immunoregulatory roles to control excessive lung inflammation following influenza infection (18).

ILCs

ILC2s are the most abundant ILC subset in the lung and facilitate the resolution of inflammation and tissue repair following virus-mediated damage (114). Following influenza virus clearance, epithelial-derived IL-33 activates ILC2s to produce several anti-inflammatory factors and type 2 cytokines, inducing a wound-healing response to promote recovery after acute lung injury (114–117). ILC2s exert pro-repair functions by restoring lung epithelial integrity and airway remodeling through a mechanism dependent on the epidermal growth factor amphiregulin (AREG) (114, 118, 119). Additionally, interferon deficiency led to host protection from lethal influenza virus infection dependent on IL-5- and AREG-producing ILC2s (118, 120). Consistent with a beneficial role for ILC2s, patients with severe COVID-19 harbored reduced levels of circulating ILC2s, the abundance of which negatively correlated with the duration of hospitalization and disease severity (121, 122). Similar findings were reported for other cohorts where patients with elevated numbers of NKG2D^{+} ILC2s in addition to increased serum IL-33, IL-5, and IL-13 levels exhibited improved outcomes in terms of length of hospitalization and risk of requiring mechanical ventilation (123). Surprisingly, however, the use of IL-13 receptor–blocking antibody diminished mortality in COVID-19 patients, potentially indicating a nuanced role of ILC2s in recovery, independent of IL-13 signaling (124). Further studies are required to elucidate the beneficial activities of pulmonary lung ILC2s and associated cytokines in the resolution of disease following COVID-19 and other respiratory viral infections. ILCs and NK cells can also produce significant quantities of IL-22, a tissue-protective cytokine that protects epithelial cells from apoptosis and triggers proliferation of epithelial cells (125). Studies in mouse models identified a critical role for IL-22-producing ILCs and/or NK cells in the promotion of inflammation resolution and expression of tissue-repair genes in the context of influenza virus infection (125–127).

T Cells

Foxp3^{+}CD4^{+} regulatory T cells (Tregs) are present in various nonlymphoid tissues, including lung tissue, poised to exert immunoregulatory functions and prevent immunopathology. Upon influenza virus infection, Tregs accumulate in the lungs and attenuate neutrophilic and monocyte-driven inflammation by secreting anti-inflammatory cytokines TGF-β and IL-10

(128, 129). In addition to Foxp3, transcriptional factors such as T-bet, Blimp-1, and IRF4 further define Treg functions in different inflammatory milieus (130, 131). The Th1-associated transcription factor T-bet is elevated in pulmonary Tregs during influenza virus infection, which in turn suppresses excessive Th1-mediated inflammation (38, 130). Similarly, Tregs produce IL-10 through IRF4-Blimp-1 signaling, thereby limiting influenza virus–induced immunopathology (38, 129, 131). In support of a protective role of Tregs, severe COVID-19 was reported to be associated with a significant decrease in circulating and airway Tregs (132, 133). However, other studies indicate an increase in circulating Tregs in severe disease, with a concomitant overexpression of suppressive molecules potentially diminishing antiviral responses (134, 135). These contradictory observations may be a function of dysregulation vis-à-vis the timing of Treg activity—compromising antiviral immunity during early stages of infection but limiting immunopathology to promote recovery following viral clearance. However, further mechanistic studies are required to uncouple these roles and identify nodes of regulation to enhance recovery in the aftermath of respiratory viral infections. Aside from the suppression of inflammation, Tregs can promote tissue repair (136). A subset of lung-infiltrating Tregs produce AREG and enhance lung healing during influenza virus infection (137). Consistent with this notion, Treg-specific AREG deficiency resulted in severe lung injury and disrupted epithelial integrity without altering Treg suppressor functions and antiviral immunity following influenza virus infection (137). Increased Notch4 expression on circulating Tregs has been associated with COVID-19 severity and predicted mortality. Mechanistically, Notch4 antagonizes IL-18 signaling, resulting in dynamically restraining AREG-dependent tissue repair, which increases severe pulmonary inflammation in respiratory viral infection (138). Notably, Tregs from aged mice demonstrated a cell-autonomous impairment of reparative programs and gain of a proinflammatory phenotype after influenza pneumonia, thus resulting in delayed resolution of inflammation (139).

In addition to Tregs, conventional effector T cells in the lung also mediate immunomodulatory functions to promote the resolution of inflammation following respiratory viral infections. Effector $CD4^+$ T cells and $CD8^+$ T cells produce high levels of IL-10 during the onset of adaptive responses following influenza virus and RSV infections, curbing excessive pulmonary inflammation, tissue damage, and mortality (38, 140, 141). Notably, IL-10 production by effector T cells requires stimulation with IL-27 and IL-2, which are typically restricted to the site of infection, suggesting that the local environment regulates effector T cell function (140, 142).

LUNG REGENERATION

A hallmark of severe respiratory viral infection is extensive destruction of the airway and alveolar epithelium due to either direct infection or collateral immunopathology. Moreover, the endothelium and mesenchyme undergo substantial remodeling, resulting in loss of the delicate microarchitecture of the alveolar epithelium. To restore homeostasis and physiological pulmonary function, diverse progenitor cells within the airway and alveolar epithelium respond to damage-associated cues such as hypoxia to regenerate cells lost during acute disease (**Figure 3**). A complex set of cellular and molecular players participate in this repair process and require strict regulation to ensure successful regeneration, as detailed below.

Airway Epithelium

The trachea and proximal airways are the interface between the external environment and the distal parenchyma, serving as a barrier to diverse insults including viruses. The production of mucus by goblet and other secretory cells as well as the ciliary beat are essential for mucociliary clearance of pathogens and debris (143). However, they are frequently infected and exhibit squamation

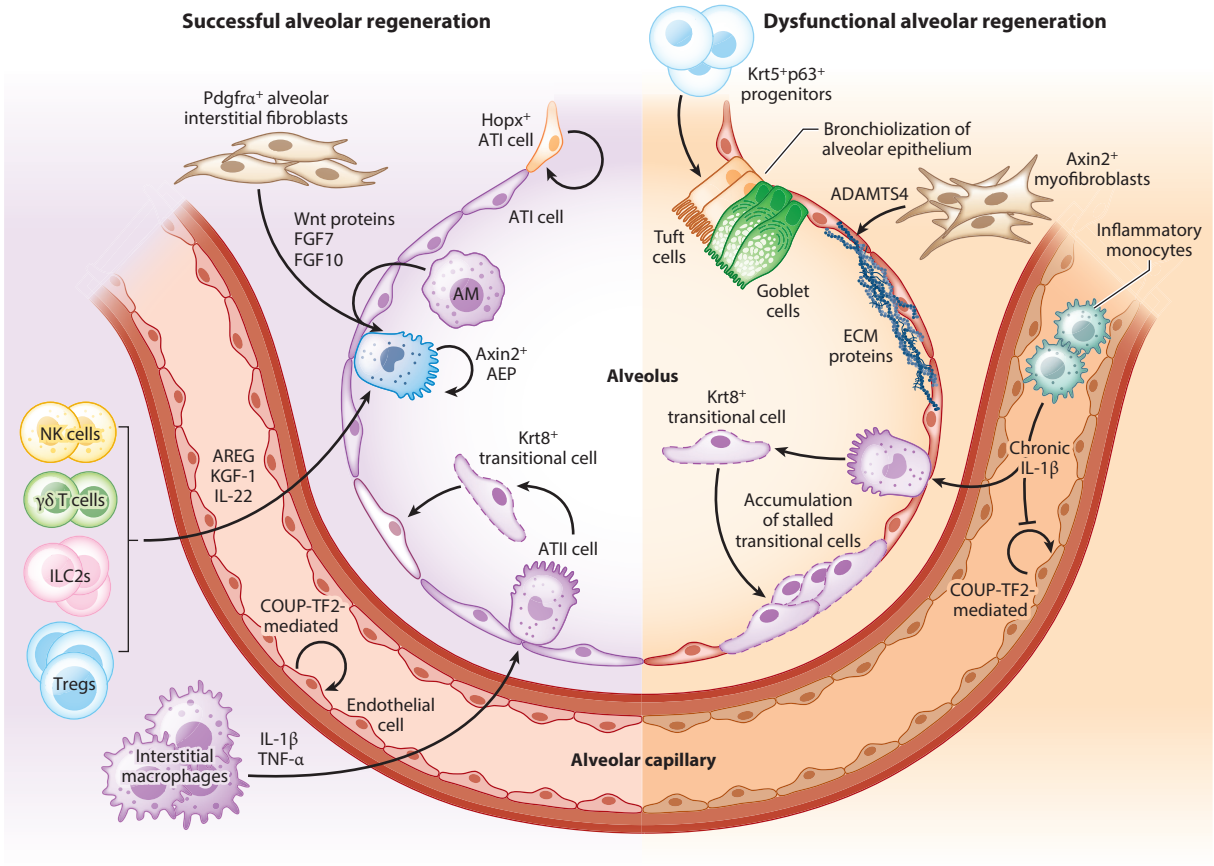

Figure 3

Alveolar regeneration following virus-induced lung injury. Successful alveolar regeneration primarily relies on a subset of ATII cells, known as alveolar epithelial progenitors. Various immune and structural cells provide essential signals, including Wnt proteins, FGF7, FGF10, IL-22, AREG, KGF-1, etc., to facilitate this process and augment epithelial regeneration. Interstitial macrophage–derived inflammatory cytokines like IL-1β and TNF-α induce ATII cells to adopt a $Krt8^+$ transitional state to ultimately differentiate into functional ATI cells. Moreover, endothelial cells further undergo self-renewal via a COUP-TF2-dependent mechanism. During severe disease characterized by exuberant inflammation and extensive alveolar damage, $Krt5^+p63^+$ progenitors are recruited from the airways, which are typically biased to adopt airway fates resulting in bronchiolization of the alveolar epithelium. Moreover, chronic inflammation results in the accumulation of $Krt8^+$ transitional cells, preventing their differentiation into ATI cells while also impeding COUP-TF2-mediated endothelial regeneration. Elevated deposition of extracellular matrix proteins and activity of pathological fibroblasts further hinder alveolar regeneration, potentially resulting in fibrosis and chronic sequelae. Abbreviations: AM, alveolar macrophage; AEP, alveolar epithelial progenitor; AREG, amphiregulin; ATI, alveolar epithelial type I; ECM, extracellular matrix; ILC2, type 2 innate lymphoid cell; Krt8, cytokeratin; NK, natural killer; Treg, regulatory T cell.

along with loss of the nascent pseudostratified epithelium during acute disease (144). In response to injury, resident cytokeratin 5–positive ($Krt5^+$) basal cells undergo self-renewal and migrate to cover damaged areas, forming a transient stratified structure (145). Subsequent differentiation, a process regulated by Notch and Myb signaling, repopulates lost secretory, goblet, and multiciliated cells and restores the pseudostratified architecture of the airway epithelium (145–148). In distal murine airways (known to lack endogenous basal cells), uninjured $Scgb1a1^+$ secretory cells

maintain club cells and multiciliated cells (149). In contrast to human intrapulmonary airways, among murine airways only the trachea and proximal bronchi harbor basal cells, an important consideration during the study of airway regeneration using mouse models (150). Additional progenitors in the distal airways have also been found to contribute to alveolar regeneration in certain contexts, as described below.

Alveolar Epithelium

Alveolar damage during respiratory infections triggers diverse repair processes to repopulate the denuded epithelium. Although quiescent during homeostasis, moderate lung injury triggers alveolar epithelial type II (ATII) cells to undergo self-renewal and transdifferentiate into ATI cells (150, 151). A distinct subset of ATII cells, termed alveolar epithelial progenitors, were found to account for the majority of ATII cell proliferation after viral injury (152, 153). The alveolar epithelial progenitors preferentially reenter the cell cycle upon activation of Axin2, downstream of Wnt signaling, to undergo self-renewal and differentiation to ATI cells. Alveolar macrophages secrete essential Wnt proteins via a Trefoil factor 2–dependent mechanism to support ATII-mediated repair (154). In addition, mesenchyme-derived FGF7 and FGF10 as well as numerous signaling pathways including Notch, TGF-β, BMP, and Hippo facilitate successful ATII cell–mediated repair (150, 152, 153).

Lineage-tracing studies have been instrumental in elucidating the crucial role of ATII cells in repopulating the ATI niche via the $Krt8^+$ ATII-ATI transitional state (155–157). Interstitial macrophage–derived IL-1β in particular, along with TNF-α, has been identified to provide an essential inflammatory niche, to promote differentiation of the transitional cells (155, 158). Given the pleotropic functions and multifaceted responses induced by these molecules, strict regulation is required, with chronic inflammation leading to accumulation of these transitional cells in pathological contexts such as fibrosis (155, 157). Additional cues from the immune system, including AREG, keratinocyte growth factor 1 (KGF-1), and IL-22 derived from ILCs, Tregs, γδ T cells and/or NK cells, augment epithelial regeneration and help restore the structural integrity of the lung following viral damage (114, 137).

In cases of diffuse alveolar damage following severe respiratory infections, the substantial loss of ATI cells leads to impaired gas exchange and potentially respiratory distress (159). The resultant hypoxia triggers activation and recruitment to the distal lung of rare $Sox2^+p63^+$ epithelial progenitors, characterized by Krt5 expression (160). Colonization of the distal lung by these progenitors is crucial for maintenance of pulmonary function during acute disease (161), likely due to preservation of the structural integrity of the distal lung. However, these progenitor cells have been found to persist in an undifferentiated state well past viral clearance, skewed toward airway fates such as goblet and tuft cells upon eventual differentiation (162). This airway bronchiolization of the distal lung is also observed in humans following severe damage and is typically associated with suboptimal repair; however, the origin of these cells remains unknown (159). Sophisticated lineage-tracing studies have revealed the ability of an additional bipotent progenitor subset termed bronchioalveolar stem cells to contribute to regeneration of both distal airway and alveolar cells (163–165). In contrast to mice, humans possess respiratory bronchioles where the distal airways interact with the alveolar niche. Recently, a secretory cell population residing in the respiratory bronchiole was identified as a source of ATII cell progenitors (166, 167). These cells, in addition to several other progenitors, contribute to repair of the distal lung following injury; however, their relevance in the context of viral injury is unclear (150). Some progenitors are also known to be preferentially targeted for viral infection, further complicating the elucidation of their respective contributions to repair (168).

Mesenchyme Remodeling

Stromal cells residing within the alveolar compartment have been demonstrated to maintain alveolar homeostasis and aid epithelial repair following injury (169). Alveolar fibroblasts secrete and replenish ECM components to provide a scaffold for epithelial and endothelial regeneration (170). Monocytes also contribute to this process by secreting several proangiogenic and matrix-remodeling enzymes (171). Moreover, ILC2-derived IL-13 is known to induce M2-like polarization of macrophages, promoting collagen synthesis and ECM remodeling (171).

Alveolar interstitial fibroblasts expressing Pdgfrα support ATII cell growth and differentiation (172, 173). These cells provide FGF7 and FGF10, essential ligands for ATII cell–mediated repair (152). A Wnt-responsive $Axin2^{+}Pdgfr\alpha^{+}$ subset of fibroblasts, termed the mesenchymal alveolar niche, initiate reciprocal paracrine signaling with ATII cells and alveolar epithelial progenitors to facilitate self-renewal (172). In contrast, an $Axin2^{+}$ myofibrogenic progenitor cell was found to seed pathological myofibroblasts, associated with excessive production of ECM components, resulting in dysplastic repair and fibrosis (172, 173). Moreover, uncontrolled activity of damage-responsive fibroblasts via ECM proteases, ADAMTS4 in particular, promoted excessive immune cell infiltration and lethal immunopathology following influenza virus infection (174). While these studies provide insight into the role of the mesenchyme in regulating functional and dysplastic epithelial repair, mechanisms governing the regeneration of mesenchymal cells lost during acute infection remain unknown, an important gap in the field.

Endothelium Regeneration

To preserve optimal gas exchange following viral/immune-mediated injury of the distal lung, regeneration of pulmonary endothelial cells in addition to the alveolar epithelium is crucial. Endothelial progenitor cells were first identified in the rat lung, where they repopulate and repair the microvasculature following injury (175). In the context of influenza virus–mediated lung injury, COUP-TF2 was identified to play a major role in regulating endothelial cell proliferation and migration (176). Notably, activation of NF-κB in endothelial cells via proinflammatory cytokines such as IL-1β and TNF-α was found to inhibit COUP-TF2 activity and subsequent repair (176). The beneficial role of these cytokines in ATII cell–mediated repair described above further confirms the requirement for strict spatiotemporal regulation of these mediators for successful repair. Recent studies using single-cell technologies have facilitated the identification of numerous pulmonary endothelial cell subsets. A $Car4^{high}$ subset in particular was found to associate with areas of alveolar damage and a transcriptional signature indicating receptiveness to cues from the alveolar epithelium (177).

CHRONIC SEQUELAE

A complex interplay of cellular and molecular mediators, including those originating from the immune system, are crucial for functional repair of the lung following viral injury. However, a variety of factors vis-à-vis the pathogen as well as the host may potentially result in dysregulation of regenerative processes, leading to aberrant repair and chronic sequelae (178, 179) (**Figure 3**). The COVID-19 pandemic in particular has highlighted this phenomenon, termed postacute sequelae of COVID-19 (PASC), with numerous reports of symptoms persisting weeks to years after primary infection (180). PASC patients exhibit a variety of symptoms, ranging from generic myalgia, dyspnea, and joint pain to specific pulmonary, neurological, and cardiovascular sequelae (180–182). This phenomenon is not unique to SARS-CoV-2. Other common respiratory viruses as well as pathogens are known to potentially result in the development of chronic pathology (179, 183). The etiology of postviral disease remains unknown, and several hypotheses are currently under

investigation (183). In particular, sustained dysregulation of the immune system has emerged as a unifying feature in driving chronic disease following various respiratory viral infections (179). The remainder of this section highlights major immune players implicated in the development of fibrotic disease following acute SARS-CoV-2 and influenza virus infections. A recent review further provides an extensive description of the immune determinants of chronic pulmonary sequelae following various respiratory viral infections (179).

Clinical studies revealed an accumulation of monocytes, DCs, and pDCs within the airways of PASC patients, which correlated with the incidence of radiological abnormalities and impaired lung function (44, 184). The accumulation of profibrotic $CD163^+$ monocyte–derived macrophages during COVID-19 ARDS further lends credence to this notion (185). Severe COVID-19 is associated with highly elevated levels of monocyte/macrophage-derived IL-1β as well as accumulation of $Krt8^+$ transitional cells, indicating dysplastic repair that further contributes to impaired pulmonary function (155, 186). Moreover, sustained upregulation of IFN-I and IFN-III was observed in PASC patients, likely disrupting epithelial repair and differentiation (70, 71, 187). Instead of resolution following acute disease, chemokines such as CXCL9, CXCL10, and CXCL11 have been observed to remain elevated in the airways of PASC patients and lead to maintenance of several adaptive cells (184, 187). The accumulation of $CD8^+$ T cells and B cells strongly correlated with impairment of pulmonary function, epithelial damage, and incidence of radiological abnormalities in PASC patients (44, 184). Notably, B cell levels did not correlate with SARS-CoV-2-specific antibody titers (184). Instead, several studies have reported autoantibodies associated with increased disease severity and subsequent development of PASC, suggesting a detrimental role of these B cells in the postacute phase of infection (188–192). Aging further elevates the risk of postviral disease, at least in part due to nonresolving inflammation driven by $CD8^+$ Trm cells, which impaired lung function and induced fibrosis, with improved outcomes upon their depletion (178, 193).

CONCLUDING REMARKS

The COVID-19 pandemic has spurred an unprecedented response in the scientific community, with widespread collaborative and interdisciplinary efforts geared toward the characterization of viral pathogenesis and immune responses and the development of therapeutics to mitigate severe disease. A consistent feature observed during COVID-19, but also other viral pneumonias including influenza, is the heterogeneity in severity of disease. While several factors underlie this, host-related factors (age, comorbidities, pregnancy, etc.) in particular are known to greatly enhance morbidity (178, 194). Overt changes in the immune system resulting from these variables, characterized in the absence of infection, are thought to contribute to this phenomenon (195). However, detailed characterization of specific immunological mechanisms dysregulated in these individuals during infection would likely yield more targeted approaches to mitigate disease.

Most investigations into the pathogenesis of respiratory viral infections have traditionally focused on the acute phase. For example, we now have a plethora of antiviral and anti-inflammatory drugs that, when used in the appropriate therapeutic window during acute disease, greatly improve prognosis and outcomes. The immense burden of chronic pulmonary sequelae, however, indicates an urgent need for the development of pro-repair therapeutics aimed at augmenting lung regeneration following injury. Furthermore, in several cases the same cellular/molecular mediator(s) elicits both protective and pathogenic effects depending on the stage and context of disease. We must now design targeted studies to uncouple these activities and downstream signaling pathways, potentially via more-detailed spatiotemporal characterization (196).

Our understanding of the communication between immune cells, epithelial cells, endothelial cells, and stromal cells during and in the aftermath of respiratory viral infections, although

improving, is relatively rudimentary. The majority of efforts by immunologists and virologists have been directed toward elucidating viral pathogenesis and host responses relevant for viral clearance. Independent studies from lung biologists have also described the process underlying the regeneration of the alveolar epithelium, endothelium, and mesenchyme following viral injury. However, the most prominent gap in our understanding relates to the communication between immune cells and various nonimmune cells within the lung during viral infection and recovery. Additionally, studies have typically relied on reductionist methodologies to identify relevant players and validate their role in the context of viral diseases. As biologists, however, we can appreciate the complex interplay of molecular and cellular mediators underlying physiological processes. Thus, although there is immense value in reductionist studies, it is critical to eventually integrate these findings and adopt holistic approaches to understand the nature of interactions within the lung and their relevance in viral pathogenesis and tissue recovery. Insights into the molecular and spatiotemporal nature of lung cellular cross talk would elucidate the determinants of functional repair, revealing novel strategies to restore the pulmonary architecture, dampen chronic sequelae, and promote host recovery.

DISCLOSURE STATEMENT

J.S. is a consultant for the Teneofour company, which does not directly involve this work. The authors are not aware of any other affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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