



Influenza virus and SARS-CoV-2: pathogenesis and host responses in the respiratory tract

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Abstract | Influenza viruses cause annual epidemics and occasional pandemics of respiratory tract infections that produce a wide spectrum of clinical disease severity in humans. The novel betacoronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in December 2019 and has since caused a pandemic. Both viral and host factors determine the extent and severity of virus-induced lung damage. The host's response to viral infection is necessary for viral clearance but may be deleterious and contribute to severe disease phenotypes. Similarly, tissue repair mechanisms are required for recovery from infection across the spectrum of disease severity; however, dysregulated repair responses may lead to chronic lung dysfunction. Understanding of the mechanisms of immunopathology and tissue repair following viral lower respiratory tract infection may broaden treatment options. In this Review, we discuss the pathogenesis, the contribution of the host response to severe clinical phenotypes and highlight early and late epithelial repair mechanisms following influenza virus infection, each of which has been well characterized. Although we are still learning about SARS-CoV-2 and its disease manifestations in humans, throughout the Review we discuss what is known about SARS-CoV-2 in the context of this broad knowledge of influenza virus, highlighting the similarities and differences between the respiratory viruses.

Influenza viruses are enveloped viruses of the *Orthomyxoviridae* family, which are classified into four genera, which include influenza virus A–D (IAV, IBV, ICV and IDV). With regard to human health, IAVs and IBVs are of main concern; ICVs are endemic and cause only mild disease in humans, and IDVs primarily cause infection in cattle¹. IBVs are restricted to humans and are classified into two circulating lineages (B/Victoria and B/Yamagata)². IAVs, the cause of the majority of annual epidemic and all occasional pandemic human disease, are further subtyped on the basis of two surface glycoproteins located within the host-derived lipid membrane of virions, haemagglutinin (HA) and neuraminidase (NA)³. Sixteen HAs and nine NAs have been described in avian species, the main natural animal reservoir of influenza viruses; two additional HAs and NAs have been described in bats^{3,4}. The IAVs H1N1 and H3N2 currently cause most epidemic disease in humans². Influenza viruses are in a constant state of evolution within animal and human reservoirs facilitated by high mutation rates due to low-fidelity RNA polymerase proofreading capabilities⁴. Cumulative changes in sequences encoding

HA and NA lead to antigenic drift in IAVs and IBVs, which alters fitness for human infection as the structure of antigenic surfaces recognized by previously protective humoral responses changes and contributes to epidemic disease⁵. HA (and to a lesser extent NA) gene segments from avian reservoirs may also reassort with contemporaneously circulating human influenza viruses to produce novel strains capable of causing pandemics, a process termed antigenic shift^{4,5}. Since 1889 there have been five IAV pandemics, the most severe of which was in 1918 and the most recent of which was in 2009 (REFS^{4,6}). IAV infection may additionally arise as an epizootic infection frequently leading to severe disease. Fortunately, thus far there has been limited human-to-human transmissibility potential demonstrated by these viruses. An example is the highly pathogenic H5N1 IAV that is associated with case fatality rates as high as 60%⁷.

Coronaviruses are enveloped single-stranded non-segmented RNA viruses of the *Coronaviridae* family, subfamily *Coronavirinae*, which are further subdivided into four genera based on phylogenetic analyses:

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alphacoronaviruses, betacoronaviruses, gammacoronaviruses and deltacoronaviruses⁸. Similarly to influenza viruses, coronaviruses circulate within non-human reservoirs. Mammalian coronavirus infection is predominantly caused by alphacoronaviruses and betacoronaviruses, which share bats and rodents as natural reservoirs^{9,10}. Avian coronavirus infections are caused by gammacoronaviruses and deltacoronaviruses, which share birds as natural reservoirs⁹. To date, seven coronaviruses associated with human coronavirus (HCoV) infections have been identified. Four (HCoV-NL63, HCoV-229E, HCoV-OC43 and HCoV-HKU1) tend to cause mild seasonal respiratory infections in otherwise healthy individuals¹¹. The other identified human coronaviruses, including severe acute respiratory syndrome coronavirus (SARS-CoV, which emerged in 2002 and was identified in 2003 (REF.¹²)), Middle East respiratory syndrome coronavirus (MERS-CoV, which emerged and was identified in 2012 (REF.¹³)) and the recently identified severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, which emerged in 2019 and was identified in 2020 (REF.¹⁴)), cause more severe clinical manifestations. Coronaviruses have the largest genome of any RNA virus¹¹ and use a replication strategy, including ribosomal frameshifting and generation of subgenomic RNAs, that predisposes to recombination events that confer the ability to develop novel host specificity^{15,16}. Indeed, after the emergence of SARS-CoV in 2003, numerous SARS-like coronaviruses were identified in bat populations¹⁷. When SARS-CoV-2 was initially sequenced in bronchoalveolar lavage fluid samples from patients identified early in the pandemic

in December 2019, the analysis demonstrated 96.2% sequence similarity to a bat coronavirus, Bat CoV RaTG13 (REF.¹⁸). Human infection with a coronavirus from its natural reservoir is thought to arise after adaptation in an intermediate host, during which time the ability for efficient human infection and human-to-human transmission develops (for example, camels in the case of MERS-CoV)¹⁰. A number of potential intermediate hosts have been proposed for SARS-CoV-2, although none has been definitively proved to date¹⁹.

In the following sections, we discuss influenza virus and coronavirus infection in humans, pathogenesis of viral infection, the contribution of the host response to severe disease and late epithelial repair mechanisms following viral infection. Although the mechanisms of SARS-CoV-2 pathogenesis are still being uncovered, throughout the Review we discuss what is known about SARS-CoV-2 and COVID-19 in the context of the wealth of knowledge of influenza virus pathogenesis, highlighting similarities and differences between these respiratory viruses.

Infection in humans

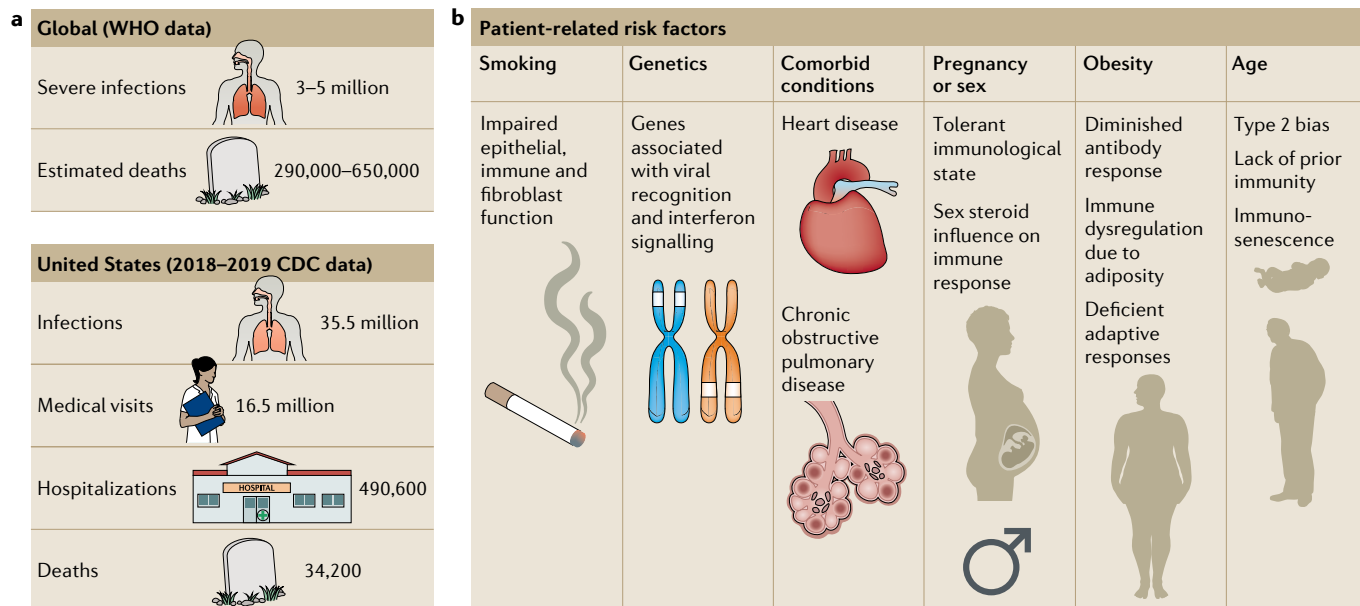
Influenza virus and disease. Human infection with influenza viruses produces a broad spectrum of clinical disease severity, which ranges from asymptomatic infection to death. Adaptive immune memory from prior exposure by either natural infection or immunization can prevent infection or limit the development of symptoms or severe complications (TABLE 1). Young children without prior exposure who are immunologically naive to influenza virus are at risk of severe disease²⁰.

Table 1 | Selected comparisons between influenza virus and SARS-CoV-2

| Parameter | Influenza virus | SARS-CoV-2 |
|--|--|--|
| Receptor usage | Sialic acid | ACE2 |
| Viral surface protein processing | Haemagglutinin processing by trypsin-like proteases | Spike protein processing by host proteases, including TMPRSS2, cathepsin L and furin, neuropilin 1 |
| Cellular tropism | Respiratory epithelial cells: types I and II alveolar epithelial cells; ciliated cells | Respiratory epithelial cells: type II alveolar epithelial cells, ciliated cells and secretory cells; sustentacular and horizontal basal cells of the olfactory epithelium Intestinal epithelial cells; endothelial cells; renal parenchymal cells |
| Tissues affected and pathology | Upper respiratory tract; lower respiratory tract (severe cases) | Upper respiratory tract; lower respiratory tract; intestinal tract; cardiovascular or endothelial system; kidneys; nervous system |
| Viral recognition in airway epithelial cells | TLR3; RIG-I; ZBP1 | TLR3; RIG-I; MDA5 |
| Site of viral replication | Nuclear | Cytoplasmic |
| Viral evasion of initial host response | NS1; PB2; PB1-F2 | NSP1; ORF6; NSP13; others? (extrapolated from other coronaviruses) |
| Extrapulmonary complications | Limited; cardiac: myocarditis (rare); neurological: encephalitis (rare) | Extensive; olfactory: anosmia; endothelial: thrombosis; neurological: stroke, encephalitis, neuropsychiatric; gastrointestinal: nausea, vomiting, diarrhoea |
| Viral evolution and antigenicity | Antigenic shift; antigenic drift | Antigenic drift? |
| Prior immunity | Previous infection; vaccination; subtype specificity | No specific SARS-CoV-2 immunity prior to late 2019–2020; protective immunity from other human coronaviruses unclear; vaccination started December 2020 |

MDA5, melanoma differentiation-associated 5; NS1, nonstructural protein 1; PB2, polymerase basic protein 2; RIG-I, retinoic acid-inducible gene I; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TLR3, Toll-like receptor 3; TMPRSS2, transmembrane serine protease 2; ZBP1, Z-DNA binding protein 1.

Influenza virus



SARS-CoV-2



Fig. 1 | Patient-related risk factors for severe influenza virus and SARS-CoV-2 infections. **a** | Estimates of yearly influenza virus infections worldwide² and in the United States (2018–2019 season)²⁵. **b** | Risk factors associated with severe influenza virus infection in epidemiological and genetic studies. **c** | Global estimated number of cases and deaths from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection⁴⁶. **d** | Risk factors identified thus far to be associated with severe coronavirus disease 2019 (COVID-19). Type 2 bias, bias towards type 2 immune responses.

Tracheobronchitis

Inflammation of the tracheal and bronchial mucosa.

Pharyngitis

Inflammation of the mucosa between the mouth and nasal cavities and the upper portion of the oesophagus (the throat).

Myalgia

Muscle ache.

Acute respiratory distress syndrome

Abrupt onset of respiratory failure characterized by inability to get oxygen into the blood owing to accumulation of lung fluid in the absence of heart failure.

The effectiveness of adaptive immune memory in preventing infection can be subtype specific, and there is evidence suggesting that the first exposure to influenza virus antigen can influence the quality of immune memory acquired over a lifetime²¹. In individuals who do become infected, complex interactions between viral and host factors influence the site of replication and the corresponding immune response, which determine disease severity. As influenza virus infections are not always medically attended owing to variability in disease manifestations, only estimates are available for yearly infection burden on a global and local basis (FIG. 1a). In a meta-analysis of human volunteer challenge studies, viral shedding is detected in most individuals on the first day after inoculation. Viral titres then peak 2–3 days

after inoculation and subsequently fall to undetectable levels by 6–7 days after inoculation. In some individuals, however, viral shedding persists for longer periods of time. Total symptom scores increase on day 1 after inoculation and generally peak by day 2 or 3 with a subsequent return to an asymptomatic baseline by days 8–9 after infection²². Most commonly, upper respiratory tract (URT) signs of tracheobronchitis and pharyngitis coupled with constitutional symptoms, including fever, malaise and myalgia, are reported by symptomatic individuals²³. However, severe disease phenotypes, including hospitalization, pneumonia, acute respiratory distress syndrome (ARDS) and death are witnessed more frequently in high-risk patient populations (FIG. 1b; TABLE 1). Multiple organ dysfunctions have been described in the case of

human H5N1 infection with evidence of viral replication outside of lung tissue, although the contribution of direct viral cytopathic effect to these extrapulmonary manifestations is unclear⁷.

A number of risk factors for complications have been identified through epidemiological studies or genomic analysis (FIG. 1b; reviewed elsewhere²⁴). Individuals >65 years or <6 months of age suffer severe outcomes of influenza virus more often than those not at the extremes of age²⁵. Immunosenescence, characterized by impaired humoral responses²⁶ and reduction in T cell receptor diversity²⁷ and T cell function²⁸ are thought to contribute to the increased disease severity witnessed in elderly populations. In infants, an immature immune system characterized by a bias towards type 2 immunity in response to infection is thought to contribute to increased disease severity early in life²⁹. Individuals with obesity suffer poor outcomes compared with lean individuals when challenged with IAV, an epidemiological observation well recapitulated in murine models³⁰. A predisposition towards severe disease in individuals with obesity is thought to be multifactorial and related to defective adaptive immune responses³¹, chronic dysfunction of inflammatory signalling related to adiposity³² and insufficient responses to annual epidemic influenza virus vaccination³³. Pregnancy increases the risk of hospitalization³⁴, which has been attributed to the development of immune tolerance as a mechanism to prevent the fetus from rejection. As a consequence, there is a shift to type 2 immunity characterized by a cytokine profile that suppresses cytotoxic T lymphocytes and alters antibody class switching to result in less effective responses to viral infections^{35,36}. Men appear to have disproportionate hospitalization rates compared with non-pregnant women³⁷, presumably related to differences in immune responses mediated by sex hormones, which may be age-dependent^{24,38}. Comorbid chronic health conditions, including metabolic syndrome³⁹, heart failure⁴⁰ and chronic obstructive pulmonary disease⁴¹, also increase an individual's risk of severe disease. Finally, environmental factors, such as cigarette smoke exposure, contribute to disease severity⁴², potentially as a result of alterations in epithelial and immune cell function⁴³ as well as in fibroblast repair responses to viral infection⁴⁴.

SARS-CoV-2 and COVID-19. Since the recognition of coronavirus disease 2019 (COVID-19; the disease caused by SARS-CoV-2), a wide range of disease severity has been described, from asymptomatic infection⁴⁵ (defined by the WHO as an infected individual who never eventually develops clinically apparent symptoms) to severe disease and death. Following its emergence, there have been >115 million cases identified and >2.5 million attributable deaths globally⁴⁶ (FIG. 1c). Symptoms arise after a median incubation period of 4.8 days, and 95% of symptomatic individuals will display symptoms by 14 days after exposure⁴⁷. A pre-symptomatic period has been defined by the WHO as an infected individual who does not presently have symptoms but who eventually manifests clinical disease. SARS-CoV-2 RNA is detected by RT-PCR in respiratory tract specimens for weeks after symptom onset⁴⁸. Peak infectivity has been

estimated to occur between 2 days before and 1 day after onset of symptoms in pre-symptomatic people⁴⁸. The most frequently identified symptom of COVID-19 is cough, followed by fever, myalgia, dyspnoea and headache. Sore throat, diarrhoea and nausea are also reported, although less frequently^{49,50}. Disturbances of smell and/or taste have been increasingly recognized as frequent symptoms of COVID-19 (REFS^{51,52}). Although loss of smell (anosmia) following viral URT infection has been recognized previously, anosmia caused by SARS-CoV-2 is potentially due to a different mechanism, which leads to clinical differences in the duration of sensory deficit^{52,53}. As seen in MERS-CoV⁵⁴ and SARS-CoV⁵⁵ infection, extrapulmonary manifestations are additionally described with SARS-CoV-2 infection (TABLE 1). These include acute kidney injury^{56,57}, skin findings⁵⁸ and thrombosis⁵⁹.

Several risk factors for severe disease have been identified in early reports detailing the clinical manifestations and outcome of COVID-19 (FIG. 1d). Genome-wide association and epidemiological studies have implicated blood type (A being higher risk than O, and Rhesus factor (Rh)-positive being higher risk than Rh-negative) as a potential heritable trait predisposing to SARS-CoV-2 infection and severe disease⁶⁰. The mechanism of potential protection afforded by blood type identified in these large population-based studies requires further investigation. Metabolic disorders such as obesity⁶¹, diabetes⁶² and kidney disease⁶³ have been associated with enhanced disease severity. Although the mechanisms remain unknown, obesity as a risk factor could be a consequence of the dampened type I interferon response found in individuals with obesity⁶⁴; one study that did not include body mass index (BMI) as a factor found individuals with severe disease requiring mechanical ventilation were more likely to have decreased type I interferon levels in the plasma⁶⁵. Cardiovascular conditions including hypertension, congenital heart disease and coronary artery disease⁶⁶ have also been linked not only with severe disease but also with exacerbation of pre-existing conditions post-recovery^{66,67}. Age has consistently been identified as an important risk factor for COVID-19 disease severity. Persons of advanced age are more likely to develop severe disease, including ARDS, during SARS-CoV-2 infection⁶⁸. SARS-CoV-2 has been diagnosed in children and adolescents of all ages, including neonates; however, disease severity is typically milder and outcome is generally more favourable than in adult individuals^{69,70}. Although correlations between disease severity caused by SARS-CoV-2 and certain pre-existing conditions are coming to light, it is important to consider that the novelty of the virus limits our ability to draw conclusions.

Pathological findings in infections

Influenza virus infection and pathology. Pathological analysis of IAV infection in humans is skewed towards a more thorough understanding of severe disease, especially when it occurs during pandemic influenza infection, on examination at autopsy^{71,72}. Owing to the preferential cellular tropism of human influenza viruses, pathological changes of the tracheobronchial

Chronic obstructive pulmonary disease
A group of diseases that restricts air movement in the lungs.

Dyspnoea
Shortness of breath.

Thrombosis
Formation of a blood clot in a blood vessel.

epithelium are characteristic (TABLE 1). With uncomplicated IAV infection in the absence of concurrent bacterial superinfection, the surface of the larynx, trachea and bronchi appear inflamed on visual inspection⁷¹. Early in infection, microscopic evaluation of tracheal and bronchial biopsy specimens demonstrates diffuse epithelial sloughing⁷¹. Mononuclear cells are the predominant inflammatory cells present⁷³; neutrophils are typically absent early, but may be present with increasing degrees of epithelial necrosis with severe disease or with the presence of a concurrent bacterial superinfection⁷². More distally, in bronchioles, nearly complete epithelial sloughing may again be present along with bloody exudate in the airway lumen, accompanied by interstitial swelling, mixed inflammatory infiltrates and small-vessel thrombosis in the bronchiolar walls⁷². Alveolar involvement generates similar general findings of epithelial necrosis and sloughing to more proximal locations but requires different repair mechanisms and leads to severe disease owing to compromised gas exchange. Proteinaceous alveolar fluid, which may be bloody, develops along with cellular debris and impairs efficient diffusion of oxygen and carbon dioxide across the alveolar–capillary interface, leading to severe clinical symptomatology^{74,75}.

SARS-CoV-2 and COVID-19. Lung pathology at autopsy following fatal SARS-CoV-2 infection frequently demonstrates diffuse alveolar damage (DAD) manifest as alveolar septal changes coupled with deposition of proteinaceous, potentially bloody, alveolar fluid, which compromises gas exchange (TABLE 1). Reactive type II pneumocytes and interstitial oedema are additionally seen⁷⁶. Neutrophils are common in the inflammatory infiltrate in the lower respiratory tract (LRT)⁷⁷. Inflammation of the bronchi and bronchioles is also found at autopsy, although less frequently than DAD. Corresponding to known areas of cellular tropism by single-cell gene expression analyses, immunohistochemistry staining for SARS-CoV-2 is seen in alveolar pneumocytes and ciliated epithelial cells. Tracheitis is also witnessed at autopsy with SARS-CoV-2 staining in submucosal glands and lymphocytes⁷⁷. As described above, COVID-19 is increasingly being recognized as a disease affecting not only the respiratory tract. Intracellular staining by immunohistochemistry for SARS-CoV-2 in renal epithelial cells has been demonstrated in individuals with kidney injury, but it is unclear whether pathological changes are a consequence of pre-existing renal conditions, virus-induced damage or a contribution of both⁷⁷. Ultrastructural evaluation by electron microscopy has additionally found SARS-CoV-2 particles in the enterocytes of the intestine⁷⁷. In autopsy specimens, SARS-CoV-2 RNA has been detected in the lung, kidney, large intestine, blood, spleen and heart, with the lowest cycle threshold (Ct) values in pulmonary tissue⁷⁷. Finally, lung tissue from individuals with COVID-19 exhibits unique vascular findings, including thrombosis, endothelial damage and abnormal angiogenesis patterns, compared with H1N1 infected or control lung tissue, as well as intracellular localization of SARS-CoV-2 particles within endothelial cells⁷⁶.

Host defence in the respiratory tract

A fundamental challenge to all hosts facing infection is achieving a balance between clearance of the pathogen and maintenance of tissue function. A robust immune response may rapidly clear the pathogen but can also cause extensive collateral damage and compromise tissue function, as described above for influenza virus and SARS-CoV-2 infection. Achieving this balance is particularly important in the respiratory tract as the host cannot survive long without sufficient gas exchange carried out by the lungs. Hosts employ different defence strategies depending on the type of pathogen, chronicity of the infection and the tissue affected. A useful paradigm for characterizing host defence strategies is in terms of disease resistance and tolerance^{78–80}. Disease resistance refers to the set of host processes that actively reduce the burden of the pathogen, which include both innate and adaptive immunity. Disease tolerance refers to a host response that acts to limit the damage in the affected tissue and support its function, thus ‘tolerating’ the pathogen burden. In the respiratory tract, a strategy of tolerance would maintain the essential function of gas exchange and blood oxygenation, and preserve the health of the host. The concepts of resistance and tolerance are often employed at a systems level, considering the host or a specific organ as a system of mechanisms that are connected⁷⁹. The respiratory system is made up of numerous compartments, including the nasal passages, trachea, bronchioles and alveoli, which carry out distinct functions in supporting respiratory health⁸¹. Complex interactions between structural and immune cells ultimately determine the type of tissue environment — resistant or tolerant. The main structural cell types in the respiratory tract — epithelial, endothelial and mesenchymal — have distinct and integral roles in generating these tissue environments (FIG. 2). Each cell type is capable of acquiring distinct activation states that promote resistance or tolerance. Integration of activation signals at both the cellular and tissue level has consequences for innate and adaptive host immune responses, which ultimately determine the outcome of infection.

The effectiveness of the host strategy in response to influenza virus or SARS-CoV-2 infection may depend on the compartment in the respiratory tract. For example, the URT, which is typically the initial site of infection and source of replication for transmission⁸², may benefit from a resistant host defence that favours a robust immune response to control viral spread. Type I and type III interferons have a crucial role in initially controlling viral replication in the URT and limiting spread to the lower airways^{83,84}. When this resistance is broken, and the virus spreads, the LRT may require a tolerant defence that favours preservation of the crucial alveolar structures that perform gas exchange. This idea is supported by studies in mouse models of influenza virus infection using strains of IAV that preferentially replicate in the URT instead of the LRT⁸⁵. Numerous survival phenotypes, due to diverse mechanisms, are independent of viral burden, indicating that rapid viral clearance is not necessary to improve disease outcome^{86–91}. In human disease, viral load in respiratory samples is neither a consistent correlate of disease severity nor a

Interstitial oedema

Fluid build-up in tissues outside of cells.

Angiogenesis

Development of new blood vessels.

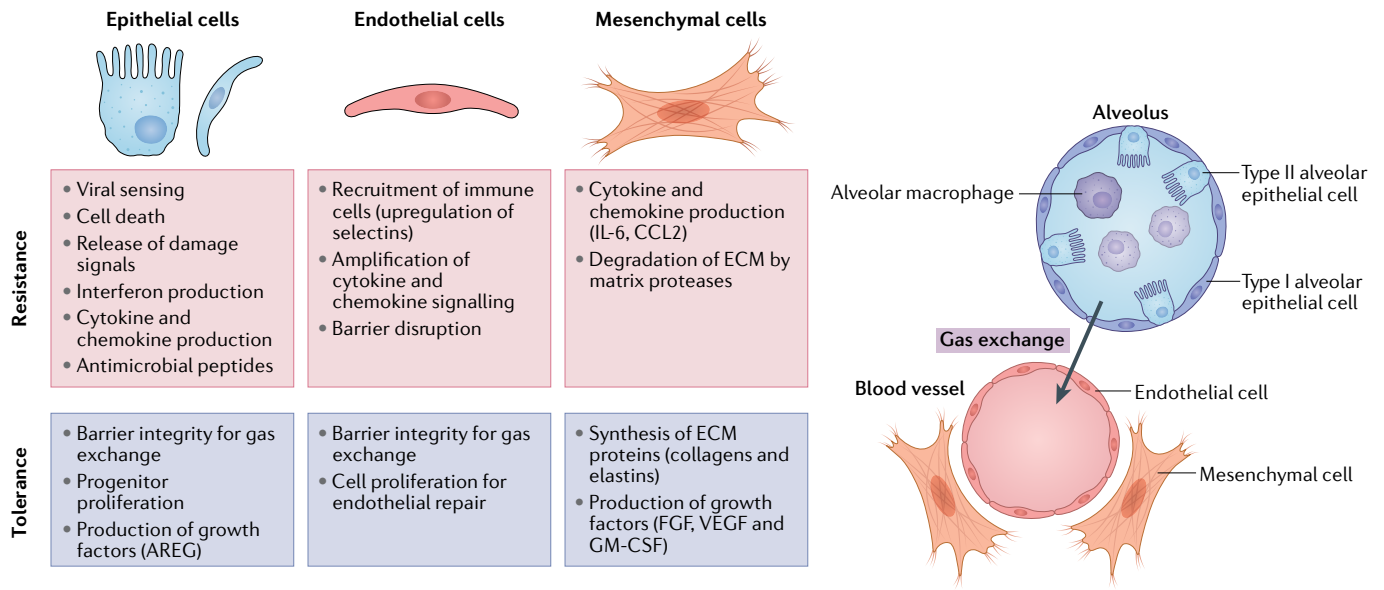


Fig. 2 | **Mechanisms of host resistance and tolerance in lung structural cells.** Recent studies have identified structural cells in the lung (epithelial, endothelial and mesenchymal) as crucial regulators of host immune responses. Cells in the lower respiratory tract must effectively communicate to promote effective viral clearance while limiting damage to endothelial cells of the blood vessels (red) and epithelial cells of the alveoli (blue), which together carry out gas exchange. Each cell type, and their phenotypically distinct subsets, contributes to disease resistance and tolerance host strategies through diverse mechanisms indicated in the boxes. The balance of these resistance and tolerance mechanisms ultimately determines the outcome and long-term consequences of respiratory viral infection. AREG, amphiregulin; ECM, extracellular matrix; FGF, fibroblast growth factor; GM-CSF, granulocyte–macrophage colony-stimulating factor; IL-6, interleukin 6.

reliable predictor of infection outcome^{92–94}. In patients with severe disease who require extended hospitalization, mortality often occurs after viral clearance, indicating that the patient continues to resist a threat that is no longer present, although there are reports of prolonged viral shedding⁹⁵.

In contrast to viral load, specific cytokines and inflammatory profiles in both serum or plasma and respiratory samples are consistently associated with the severity of infection, including in SARS-CoV-2 infection^{96,97}. High systemic levels of multiple cytokines, and their association with severity, have frequently been referred to as a ‘cytokine storm’⁹⁸. Although the term cytokine storm has become popular to describe an exuberant immune response during influenza virus infection, few studies have identified specific mechanisms regulating excessive production of inflammatory molecules that could be targeted by therapeutics. Framing the host response as a cytokine storm may be the result of a focus on systemic cytokine levels measured in serum or plasma from humans. Peripheral blood is easier to sample than the LRT and is amenable to longitudinal sampling in patients. However, it is still unclear whether specific inflammatory molecules drive lung pathology or serve as correlates of other tissue-level mechanisms. In studies that have compared respiratory compartment and peripheral blood cytokine levels, poor correlations are often observed⁹⁴. Interestingly, animal models, which allow for in-depth sampling of respiratory compartments, have identified tissue-resident non-immune and immune cells as crucial regulators of this exuberant response^{99,100}.

The following section will highlight recent studies that have begun to define the compartment-specific

mechanisms that prevent or contribute to lung damage following influenza virus infection. Migrating and tissue-resident immune cells certainly have an important role in driving lung pathology, and mechanisms have been reported for many different types of cell, including neutrophils, monocytes/macrophages and T cells. Several reviews have summarized the role of immune-cell-driven lung damage during influenza virus infection^{80,101}. In the following section, we focus on the role of non-immune structural cells that serve as upstream regulators of the host response. Studies of structural cells, including epithelial, endothelial and fibroblast cells (FIG. 2), have primarily reported on their roles in lung function by providing structural support to the tissue or maintaining the barriers required for gas exchange. These studies have underestimated their participation in the inflammatory response. However, it is now becoming clear that these cells have crucial roles in actively coordinating the host immune response to viral infections¹⁰². Lung structural cells have many of the same tools as immune cells to respond to infection, including viral sensors, cytokine or chemokine receptors, and antiviral proteins that directly inhibit replication.

Initial response of epithelial cells to influenza virus and SARS-CoV-2. Epithelial cells are the primary targets of influenza virus¹⁰³ and are the best-studied structural cells in the context of influenza virus infection (TABLE 1). The type of epithelial cells present and their relative abundance change drastically moving from the trachea to the bronchioles and eventually to the alveoli. As conducting airways, the trachea and bronchioles are rich in

mucin-producing goblet cells, mucin and antimicrobial protein-producing submucosal gland cells, secretory club cells and ciliated cells that function to move mucus along the respiratory tract^{81,104}. The alveoli are made up of thin type I pneumocytes that facilitate gas exchange and cuboidal type II pneumocytes that produce surfactant and serve as progenitor cells^{81,105}. Influenza virus cellular tropism, as well as host specificity, is determined by HA and NA, which interact with epithelial cell surface sialosaccharides that contain a sialic acid (SA) residue linked to a galactose (Gal)¹⁰⁶ (FIG. 3a; TABLE 1). Preferences in HA binding to specific SA–Gal linkages in sialosaccharides on epithelial cell surfaces contribute to host species restriction, transmissibility and clinical symptomatology^{107–109}. Whereas avian and equine influenza viruses prefer to bind SAs linked to galactose by α 2,3 linkage (SA α 2,3Gal), human influenza viruses bind SAs linked to galactose by α (2,6) linkage (SA α 2,6Gal)¹⁰⁹.

SA α 2,3Gal and SA α 2,6Gal are distributed along a gradient on the surface epithelial cells along the length of the human respiratory tract¹¹⁰. SA α 2,6Gal predominates in the nasal mucosa, sinuses, trachea and bronchi; it is also present on epithelial cells of the respiratory and terminal bronchioles. Conversely, SA α 2,3Gal molecules are primarily found on the surface of alveolar epithelial cells and rarely in the URT¹¹⁰ (FIG. 3a). Tropism for SA α 2,3Gal, which predominates in the LRT, is thought to contribute to the high pathogenicity of epizootic avian IAV infections in humans. Despite the preferential binding noted in the above work, human IAVs are able to infect type I alveolar epithelial cells¹⁰⁷.

Similarly to SARS-CoV, SARS-CoV-2 relies on angiotensin converting enzyme 2 (ACE2) and a host protease for host cell entry (FIG. 3b; TABLE 1). ACE2 is a transmembrane carboxypeptidase involved in processing angiotensin II, among other signalling proteins. It is constitutively released from the surface of airway epithelial cells as a soluble form (sACE2), which retains proteolytic activity, by the sheddases A disintegrin and metalloproteinase 17 and 10 (ADAM17 and ADAM10)¹¹¹. The spike (S) protein on the surface of the SARS-CoV-2 particle binds to ACE2 and requires activation by a host protease. Transmembrane serine protease 2 (TMPRSS2) is the most commonly implicated¹¹². Other proteases may also have a role, including cathepsin L¹¹³, which is involved in SARS-CoV entry¹¹⁴, neuropilin 1 (REF.¹¹⁵) and furin¹¹⁶. The involvement of multiple host proteases in viral entry may broaden tropism. Single-cell gene expression analyses in both non-human primates and humans have demonstrated overlapping transcription *ACE2* and *TMPRSS2* throughout the body. In the respiratory tract, overlapping expression is seen in cells of the olfactory, nasal and bronchial epithelial surfaces as well as in alveolar type II epithelial cells^{52,117–119}. For SARS-CoV-2, there is likely a gradient of infectivity along the respiratory tract with susceptible epithelial cells with high *ACE2* and *TMPRSS2* expression more abundant in the nasal epithelium of the URT than in distal regions of the lung¹²⁰. Outside of the respiratory tract, sites of *ACE2* and *TMPRSS2* expression and potential viral replication include superficial cells of the conjunctiva, enterocytes of the ileum and colon, and the gallbladder, among others^{117–119}, which may account for extrapulmonary clinical manifestations of SARS-CoV-2 (TABLE 1), although further work defining the mechanistic pathophysiology of this association is required.

Despite being the initial and primary cell type infected by respiratory viruses, infected epithelial cells and bystander epithelial cells initiate carefully regulated responses to both cell-intrinsic and extrinsic signals. Epithelial cells are equipped with many of the same host defence tools that professional immune cells are well known for, including viral sensors, direct antiviral molecules and inflammatory mediators, such as type I/III interferons, tumour necrosis factor, interleukin 6 (IL-6) and other chemokines (for example, CXCL10 and IL-8)^{100,103}. Indeed, in vitro models using influenza virus infection of normal human bronchial epithelial cells have demonstrated that epithelial cells are capable of producing inflammatory cytokines in the absence of other

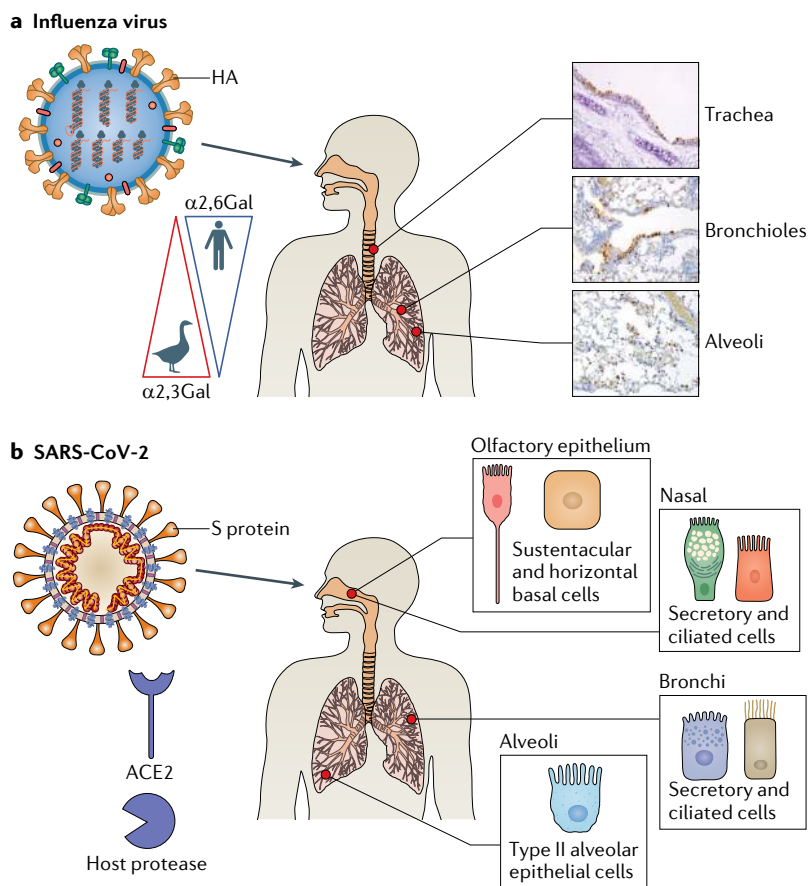


Fig. 3 | Cellular tropism of influenza virus and SARS-CoV-2. a | The haemagglutinin (HA) protein of influenza viruses preferentially binds sialosaccharides on the surface of pulmonary epithelial cells. Whereas human influenza viruses prefer sialic acids (SAs) linked to galactose by α (2,6) linkage (SA α 2,6Gal), avian influenza viruses prefer SA α 2,3Gal. These are distributed in a gradient in the human respiratory tract. Immunohistochemistry staining demonstrates intracellular localization of influenza viruses in epithelial cells at three sites from mice challenged with influenza A virus. **b** | The spike (S) protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binds angiotensin-converting enzyme 2 (ACE2) on the surface of certain olfactory and respiratory epithelial cells distributed along the human respiratory tract after activation by a cellular protease, such as transmembrane serine protease 2 (TMPRSS2) (other proteases, including cathepsin L, neuropilin 1 and furin are involved in activation). Histopathological images in part **a** courtesy of P. Vogel.

professional immune cells¹⁰³. The epithelial influence on the immune response begins early. Upon infection, the influenza virus HA protein binds to surface sialosaccharides to initiate receptor-mediated endocytosis of the virion, which subsequently fuses with the endosomal membrane and releases viral ribonucleoproteins (vRNPs) into the cytoplasm. vRNPs are trafficked to the nucleus where replication occurs. Pathogen-associated molecular patterns in the form of viral nucleic acids are recognized by the pattern recognition receptors retinoic acid-inducible gene I (RIG-I) and Toll like receptor 3 (TLR3)^{80,86,121–124} (TABLE 1). TLR7 is also important for endosomal recognition of IAV in some immune cells^{125,126}. An additional early mediator of the epithelial response to IAV infection is NLR family pyrin domain containing 3 (NLRP3), which forms a complex with other proteins termed the NLRP3 inflammasome that functions to moderate immunopathology^{86,123}. The initial signalling cascades necessary for a coordinated host response to influenza virus entry culminate in the production of hundreds of interferon-stimulated genes (ISGs) and pro-inflammatory cytokines via activation of the transcription factors interferon regulatory factor 3 (IRF3) and nuclear factor κ B (NF- κ B). Interestingly, influenza viruses encode proteins, such as nonstructural protein (NS1)¹²⁷ and polymerase basic protein 2 (PB2)¹²⁸, among others, that interfere with interferon signalling at multiple steps. Although the initial epithelial response to SARS-CoV-2 requires more study, on the basis of recently published data and knowledge extrapolated from other coronaviruses, it is likely that TLR3, RIG-I and RIG-I-like receptor melanoma differentiation-associated 5 (MDA5) also participate in innate sensing of intracellular SARS-CoV-2 and are intrinsic to induction of interferon signalling pathways^{129–132} (TABLE 1). Recent evidence suggests that the NLRP3 inflammasome is also activated in response to SARS-CoV-2 infection in CD14⁺ lung cells obtained from deceased individuals as well as in peripheral blood mononuclear cells¹³³.

Activated interferon pathways and their pleiotropic effects highlight the importance of balancing defence strategies of resistance and tolerance. As two studies recently demonstrated in mice, persistence of antiviral signalling in particular in the LRT during viral inflammation may oppose proliferation of epithelial cells, which are crucial for tissue repair and restoration of lung function^{90,91}. Thus, compartmentalization of interferon and careful regulation of timing are likely crucial to surviving a severe respiratory infection. As in the case of other coronaviruses¹³⁴, the type I interferon response to SARS-CoV-2 may be crucial. Decreased type I interferon levels in peripheral immune cells was associated with severe disease despite increased interferon- α in the lung⁶⁵. Loss-of-function variants of TLR7 resulted in a decrease in type I interferon signalling and decreased levels of interferon and ISG mRNA¹³⁵. Similarly, the presence of neutralizing autoantibodies targeting type I interferons was associated with onset of severe disease¹³⁰. Finally, compared with individuals with influenza virus, individuals with COVID-19 demonstrate downregulation of interferon signalling pathways in subsets of

peripheral blood mononuclear cells¹³⁶. As in the case of influenza virus, SARS-CoV-2 also produces proteins that interfere with interferon signalling¹³⁷ (TABLE 1).

In addition to an interferon and pro-inflammatory response to infection, altruistic programmed cell death (PCD) is an essential component of the initial cellular response to IAV infection. In benefit to the host, PCD serves to limit viral replication and prevent pathological immune responses^{138,139}. However, because there appears to be a threshold of alveolar type I epithelial cell loss of 10%, beyond which gas exchange and survival are impaired⁸⁵, it is imperative for host survival that PCD responses to prevent continued viral replication are contained¹³⁹. PCD pathways are intertwined with various levels of crosstalk, which may lead to significantly different inflammatory outcomes with imbalances or preferential activation of one pathway over another^{139,140}. Whereas necroptosis and pyroptosis are inflammatory forms of PCD that result in the release of damage-associated molecular patterns that serve to propagate inflammatory responses, apoptosis is a relatively anti-inflammatory form of PCD^{140,141}. In the context of IAV infection, Z-DNA binding protein 1 (ZBP1), which recognizes Z-RNA, has an integral role in mediating PCD responses^{124,142–144}. Immediately downstream of ZBP1 is receptor interacting protein kinase 3 (RIPK3), which contains a RIP homotypic interaction motif (RHIM) domain complementary to the ZBP1 RHIM^{124,145}. Following ZBP1-dependent RIPK3 activation, necroptosis is mediated by mixed lineage kinase domain-like (MLKL) disruption of the plasma membrane after phosphorylation by RIPK3 (REFS^{146,147}) while apoptosis is mediated by RIPK3 interaction with a complex of proteins that includes receptor interacting protein kinase 1 (RIPK1), Fas-associated via death domain (FADD) and caspase 8 (REF¹⁴⁸). It was previously unclear whether both pathways were simultaneously activated in an individual cell or whether they were mutually exclusive. Recently, using a knock-in model in which caspase 8 was engineered to be unable to signal for apoptosis, but still able to carry out its other functions necessary for animal viability, it was demonstrated that necroptosis and apoptosis fates are mutually exclusive events following IAV infection within an individual cell¹⁴⁹. Beyond influenza viruses directly activating these PCD pathways, it is important to note that interferons also lead to increased expression of many genes involved in cell death, including *ZBP1* and *MLKL*^{144,150}. Furthermore, proteins produced by influenza viruses themselves, such as PB1-F2, may induce apoptosis¹⁵¹. Early evidence suggests that SARS-CoV-2 results primarily in apoptosis of infected human airway epithelial cells¹⁵². Additionally, SARS-CoV-2 encodes the protein ORF3a, which has been shown to induce epithelial cell apoptosis dependent on caspase 8 activity, although to a lesser degree than SARS-CoV ORF3a¹⁵³.

By releasing inflammatory mediators or other bioactive molecules, either as a result of PCD or by active secretion, epithelial cells help to define the tissue microenvironment. In addition, epithelial cells produce molecules that promote tissue repair and tolerance by interacting with diverse cell types in the LRT.

One of these key molecules is granulocyte–macrophage colony-stimulating factor (GM-CSF). During IAV-induced lung injury, alveolar type II epithelial cells are primary producers of GM-CSF in the distal lung¹⁵⁴. GM-CSF not only has well-documented roles in promoting inflammatory responses by inducing proliferation and differentiation of myeloid cells, but also helps maintain epithelial barrier integrity by promoting the activity of alveolar macrophages, enhancing adaptive responses through dendritic cell activity, or acting directly on epithelial cells¹⁵⁵. Another important molecule is amphiregulin (AREG), a member of the epidermal growth factor family of molecules, which is capable of inducing both cell proliferation and differentiation¹⁵⁶. A number of studies in mice have demonstrated that AREG has a protective effect during influenza virus infection and that multiple different cell types, including both immune and parenchymal cells, can produce the molecule^{157,158,159}. Although it is unclear which cell type is the primary source of protective AREG during influenza virus infection, epithelial cells are a likely candidate^{157,159}.

Epithelial cells can also alter the tissue microenvironment through regulation of surface molecules and communication with nearby cells. One example is the upregulation of class I major histocompatibility complex (MHC) molecules that present viral peptides to CD8⁺ T cells. Influenza virus-specific CD8⁺ T cells recognize the peptide–MHC complex and release cytolytic molecules to kill the infected cell¹⁶⁰. This cell killing can further amplify the immune response through the release of inflammatory molecules from the infected cell. Killing of both infected and bystander alveolar type II cells by CD8⁺ T cells can drive acute lung damage and compromise tissue function^{161,162}.

Epithelium-derived cell adhesion and integrin molecules, which mediate cell–cell and cell–extracellular matrix (ECM) interactions and can activate other extracellular molecules, also regulate the host response during influenza infection. One example is the epithelium-specific $\alpha\beta6$ integrin, which is upregulated during infection and can modulate the lung microenvironment and collagen deposition through the regulation of transforming growth factor- β and type I and III interferon signalling^{89,163}. $\beta6$ integrin-deficient mice are unable to form the functional $\alpha\beta6$ homodimer and as a consequence have increased interferon signalling, activated alveolar macrophages and enhanced repair, resulting in greater protection from influenza virus and other respiratory pathogens⁸⁹. This protection extends to high-risk populations¹⁶⁴. Although epithelial cells are the most studied structural lung cell involved in host response to influenza virus infection, other structural lung cells have important roles in the response to and, therefore, outcome of infection.

Mesenchymal cells. Mesenchymal cells are a broad group that encompasses fibroblasts, smooth muscle cells, pericytes and other stromal cell types in the respiratory tract. These cells make up the connective tissue in the lung and exhibit diverse functions including regulation of the ECM, production of growth factors, cytokines and chemokines, and the generation of stem cell niches,

among others¹⁶⁵. As cells of the connective tissue, mesenchymal cells define the tissue environments by generating the ECM and providing signals to nearby cells, which determine their migration, proliferation and differentiation. These functions have been well studied during lung homeostasis but have not been well defined during acute respiratory infection, despite the fact that they communicate with essentially every cell type in the lung either through direct cell–cell interactions or through the ECM. One of the crucial tools that mesenchymal cells use to define the tissue environment is ECM proteases. Mesenchymal cells produce an impressive array of proteases and glycosidases that degrade or modify specific components of the ECM, including structural proteins, cytokines or growth factors, and other proteases¹⁶⁶. ECM proteases regulate each stage of lung injury or infection by degrading ECM barriers to facilitate cell migration through the tissue, activating cytokines and growth factors, and modifying the ECM during repair. Bioactive degradation products of the ECM, often referred to as matrikines, can further amplify lung inflammation by stimulating nearby cells¹⁶⁷. Several studies in mouse models of influenza virus infection have found that ECM proteases, including members of the matrix metalloproteinase (MMP) and A disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) family members, have both pathogenic (MMP9, MMP14 and ADAMTS4) and protective functions (ADAMTS5) by degrading diverse ECM proteins^{168–171}. Studies in human cases of influenza virus infection have also established correlations between the levels of ECM proteases and the severity of disease and respiratory failure¹⁷². Mechanistic studies in mice have demonstrated that the activity of specific proteases can compromise lung function by directly altering the ECM structure and relatedly by regulating immune cell migration to the site of infection or damage. Although both immune and structural cells produce ECM proteases, recent evidence suggests that mesenchymal cells are the primary producers of proteases that contribute to pathogenesis. One crucial protease is the versican-degrading enzyme ADAMTS4. During influenza virus infection, inflammatory fibroblasts produce ADAMTS4, promoting robust CD8⁺ T cell infiltration into the lung tissue. In both paediatric and adult cases of influenza virus infection, protein levels of ADAMTS4 in the lower respiratory tract were strongly associated with respiratory failure and mortality¹⁷³. Thus, fibroblasts serve as gatekeepers of immune cell access to the tissue and their exuberant inflammatory activity can drive lung damage and respiratory failure.

In addition to ECM remodelling activities, mesenchymal cells produce growth factors that directly stimulate epithelial cells to promote tissue repair. In mice, fibroblast growth factor 10 (FGF10), produced by lung mesenchymal cells, has a protective role following severe IAV infection by stimulating a subset of epithelial progenitor cells to undergo proliferation¹⁷⁴. Taken together, these studies identify lung mesenchymal cells as crucial regulators of disease resistance and tolerance and of the transition between resolution of inflammation and initiation of tissue repair.

Extracellular matrix
An intricate supportive collection of proteins and other macromolecules present in all tissues.

Endothelial cells. Pulmonary endothelial cells make up another barrier that is essential for gas exchange and lung function. The endothelium not only moves blood into the lung for oxygenation but also helps to circulate inflammatory molecules and migratory immune cells. During influenza virus infection, the endothelium becomes activated as cells upregulate surface expression of cell adhesion molecules, including P- and E-selectins⁷⁴. The endothelium is the entry point for immune cells migrating to the lung tissue. Migrating immune cells interact with cell adhesion molecules on endothelial cells and traverse this barrier on the way to the site of infection. Activation of the endothelium and extravasation of immune cells from blood capillaries into the alveoli can result in vascular permeability and an increase in fluid in the lungs¹⁷⁵. Thus, endothelial cells are also important decision-makers in determining resistant and tolerant tissue environments as they balance recruitment of immune cells to clear infected cells with integrity of the vasculature. Although human and avian influenza viruses can infect primary human endothelial cells *in vitro*^{176–178}, the extent to which they productively infect endothelial cells *in vivo* remains controversial^{174,179}.

Whether or not endothelial cells become productively infected *in vivo*, they do respond robustly to infection. In addition to upregulating adhesion molecules to recruit immune cells, endothelial cells have a crucial role in amplifying cytokine and chemokine production, which can lead to lethal immunopathology⁹⁹. The sphingosine 1-phosphate 1 receptor (S1P1R), which binds to lipid metabolites, regulates this excessive cytokine production, and agonism of S1P1R with small molecules can significantly reduce cytokine levels in the lung^{99,180}. Amplification of inflammation in endothelial cells depends on signalling through the IL-1 receptor and is independent of endosomal or cytosolic sensing of the virus. Dependence on IL-1 receptor signalling suggests that endothelial cells respond to damage signals released from epithelial cells, such as IL-1 α , or those produced by professional immune cells, likely IL-1 β ¹⁸¹.

Like the other major structural cell types in the lung, endothelial cells exhibit heterogeneity based on compartment (microvascular, macrovascular or lymphatic). Single-cell gene expression studies have begun to characterize this heterogeneity during influenza virus infection, identifying groups of cells with distinct transcriptional responses that are highly proliferative and involved in tissue repair¹⁸². The tolerogenic potential of pulmonary endothelial cells has been largely unexplored.

As described above, SARS-CoV-2 infection appears to involve the pulmonary endothelium more than other respiratory viruses, such as influenza virus. Observations of severe COVID-19 in humans indicate extensive endothelial cell activation, thrombosis and angiogenesis^{76,183,184}. This endothelial activation and thrombosis has also been observed in a non-human primate model of SARS-CoV-2 infection¹⁸⁵. The mechanisms leading to such extensive endothelial involvement are unclear, but possibilities include direct infection of endothelial cells¹⁸³ and microvascular complement protein deposition¹⁸⁶. During infection in humans, endothelial cells express

ACE2 (REF.⁷⁶), and the virus readily infects human blood vessel organoids¹⁸⁷.

Lung repair and recovery from infection

Tissue repair in the respiratory tract presents a challenge because of its distinct compartments, the diverse cell types affected and the heterogeneity of infection¹⁸⁸. A pair of excellent, recent reviews have detailed the contribution of different subsets of structural cells, including epithelial, endothelial and mesenchymal, to tissue repair and the complex crosstalk between these cells during both pathogen-induced and sterile lung damage^{188,189}.

An important theme that has emerged in studies of tissue regeneration during influenza virus infection is that the severity of infection and extent of lung damage determine which progenitor cells mobilize in response to injury and the quality of the repair that they mediate^{105,190–194} (FIG. 4). Fortunately for the influenza virus field, severe influenza virus infection in mice has become a popular model for lung biologists to study acute lung injury and repair. In general, local proliferation of alveolar epithelial progenitor cells (AEPs), which are alveolar type II cells, mediate rapid and effective repair by differentiating into both alveolar type I and type II cells^{105,195,196}. The stemness of the AEPs is maintained by WNT signalling in a close alveolar niche^{165,195,196}. This type of repair typically occurs when there is localized damage to the alveoli. However, when there is more extensive alveolar damage and severe influenza virus infection ablates alveolar type II cells, including the AEPs, alternative progenitor cell populations fulfill this regenerative role¹⁸⁸. In mice, several different alternative progenitor cells have been identified, termed bronchioalveolar stem cells, lineage-negative epithelial progenitors (LNEPs) — also known as distal airway stem cells (DASCs) — and another group of club-like epithelial progenitors^{174,190,191,194,197–199}. Several recent studies indicate that IAVs preferentially infect club-like epithelial progenitors, which express stem cell antigen 1 (SCA1) and elevated levels of MHC class I^{174,194}. Although these cells are able to facilitate alveolar epithelial repair following sterile lung damage, viral infection of the club-like progenitors may limit their ability to participate in effective tissue repair following severe IAV infection, requiring alternative progenitors to take on this role.

One of the apparent consequences of mobilizing LNEPs and/or DASCs is that they do not fully differentiate into alveolar type II cells, leaving areas of the lung with cyst-like structures with cytokeratin 5 (*KRT5*) expression and persistent pathology^{190,192,193}. In these areas of the lung that never fully repair, hypoxia drives NOTCH signalling, which prevented differentiation of *Krt5*⁺ cells into alveolar epithelial lineages in mice¹⁹³. Areas of persistent pathology maintain distinct microenvironments with gene expression signatures of type 2 immunity and the presence of tuft-like cells^{200,201}. The physiological consequences of these signatures and the extent to which this happens in severe influenza virus infection in humans is unknown. It should be noted, however, that ongoing lung dysfunction, evident by both lung imaging and pulmonary function testing, has been described following severe IAV and SARS-CoV-2 infection^{202–204}.

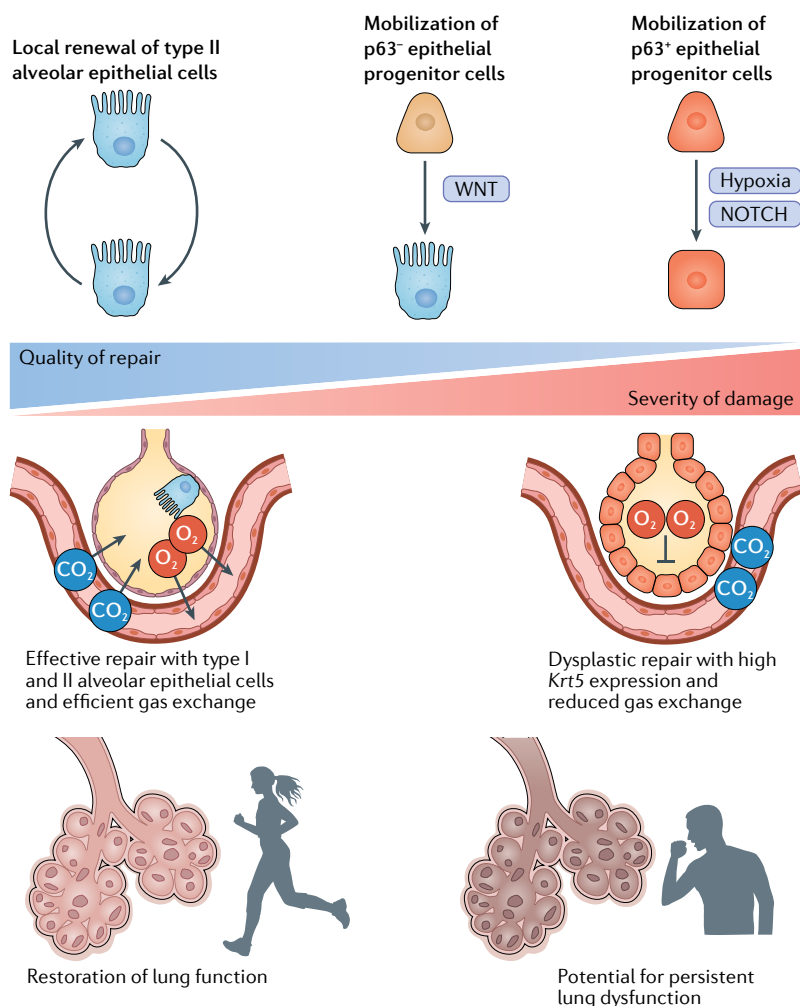


Fig. 4 | Alveolar epithelial repair along the severity continuum. The regeneration of alveolar tissue and restoration of function is essential for survival following a severe respiratory infection. Recent studies have demonstrated that the extent and severity of influenza virus infection determines the quality of alveolar epithelial repair. Repair by self-renewing type II alveolar cells occurs during less severe infection and is efficient. During infection with extensive tissue damage when type II alveolar cells are ablated, additional epithelial progenitor cells (p63⁻ and p63⁺) mobilize to mediate repair. WNT and NOTCH signalling pathways determine localized differentiation of these progenitor cells. In severe damage, mobilization of p63⁺ progenitors can result in dysplastic alveolar repair characterized by the formation of cyst-like structures with high expression of *Krt5* leading to reduced lung function. This dysplastic repair may lead to persistent lung dysfunction.

Together, these exciting advances define the mechanistic basis for how the extent and severity of infection determine the quality of tissue repair following influenza virus infection and provide a foundation for developing both cellular and molecular therapies to influence the trajectory of lung regeneration.

Experimental models of SARS-CoV-2

The complexities of the host response to SARS-CoV-2 necessitate *in vivo* studies, and it is crucial to consider both pathogenesis and transmission when modelling a novel disease (TABLE 2). Initial reports have described SARS-CoV-2 infection in rodents, ferrets, non-human primates and cats^{205–207}; however, it is unclear which model best recapitulates human infection. Mice are

not susceptible to SARS-CoV-2 owing to the inability of murine ACE2 to bind the viral spike protein. Therefore, infection of mice requires either introduction of the human ACE2 receptor or adaptation of SARS-CoV-2 to the murine receptor²⁰⁸. Human ACE2 transgenic mouse lines have been developed with different promoters driving *ACE2* expression. The tissue distribution and abundance of human *ACE2* expression differ between these transgenic lines and in part determine the severity of disease being modelled²⁰⁸. In mice in which *ACE2* expression is driven by the epithelial cytokeratin 18 promoter, unadapted SARS-CoV-2 causes severe pathology and respiratory distress^{209,210}; however, recently reported mouse-adapted strains also cause severe disease in BALB/c mice^{211,212}. Ferrets, the gold-standard model for influenza virus transmission studies, also transmit SARS-CoV-2 by both direct and respiratory contact²¹³. However, disease severity is mild, and viral replication is generally restricted to the URT^{205,208}. Pathogenesis in non-human primates varies by species. African green monkeys develop acute pneumonia and lung injury persisting for >1 month despite viral clearance²⁰⁷, whereas rhesus macaques manifest pulmonary infiltration similar to humans with only mild to moderate disease severity²⁰⁶. Interestingly, hamsters can efficiently transmit SARS-CoV-2 (REF.²¹⁴) and experience severe disease including weight loss, DAD and high viral load in the alveolar space²¹⁵. As in the human experience, aged animals, including BALB/c mice²¹¹ and Syrian golden hamsters²¹⁶, demonstrate more severe clinical manifestations of infection. Because human SARS-CoV-2 disease severity is variable, *in vivo* systems spanning the spectrum of disease could prove invaluable.

Outlook: current and potential therapies

At both the individual and community level, annual seasonal influenza virus vaccination remains a mainstay of influenza control. However, several considerations make reliance on vaccination alone inadequate. In certain populations at high risk of severe complications from influenza virus infection (that is, elderly individuals and individuals with obesity) vaccine response is less robust. Antigenic drift may reduce vaccine efficacy at population level, placing large communities at risk. Finally, antigenic shifts resulting in pandemic influenza virus as well as epizootic infections with highly pathogenic strains of IAV are not covered by vaccines and may result in severe disease in large numbers of individuals. For these reasons, the availability of effective therapies for influenza virus is crucial. Aside from supportive care to correct physiological derangements, the currently available treatments are all antivirals. Those available are well tolerated and shorten symptom duration, although are most efficacious when given early.

Currently available therapeutics for influenza virus infection are antiviral compounds (BOX 1), many of which need to be started in the first 2–3 days of infection (when viral replication is at its peak) to demonstrate benefit. As described above, severe influenza (as well as COVID-19) results in profound disruption of lung integrity, which is only in part driven by viral

cytopathic effect. In severe infections, deleterious immune responses and inadequate repair mechanisms contribute to disease outcomes. Given the short therapeutic window for antivirals, targeting host factors that drive excessive inflammation and immunopathology offer a promising alternative treatment strategy. Any host therapeutic aimed at reducing lung injury, however, must consider the potential negative effect of delaying viral clearance and leaving patients with severe disease vulnerable to secondary infections. Broadly immunosuppressive agents, such as corticosteroids, are frequently given to patients in other scenarios to reduce inflammation, but are not recommended as treatment for influenza infection, unless a separate indication for their use exists²¹⁷. However, in the case of SARS-CoV-2 infection leading to hospitalization, dexamethasone (a corticosteroid) given for a median of 7 days (up to 10 days) has been shown to reduce mortality, which was most evident in patients requiring higher levels of support at randomization²¹⁸.

As broadly acting immunosuppressants do not appear efficacious in the case of influenza virus infection and have potentially harmful side effects, more targeted therapeutics are needed that modulate specific immunological pathways. Ideally, these agents would target host factors that are active at the site of infection or injury and would avoid systemic effects. Recent work on the role of lung structural cells in determining tissue resistant or tolerant states has identified several promising classes of cellular and molecular targets. Each of the main structural cell types (mesenchymal, endothelial and epithelial) has a distinct role in determining local tissue environments that could be modulated to maintain tissue function. Mesenchymal cells are professional tissue remodellers and produce key lung ECM proteases that drive immunopathology by causing direct damage to the lung structure and regulating the movement of immune cells^{168,169}. Inhibitors that selectively target these proteases may promote tissue tolerance by preserving lung integrity for gas exchange and preventing colonization

Table 2 | Animal models of influenza virus and SARS-CoV-2 infection and pathogenesis

| Animal | Physiology and genetics | Influenza virus | SARS-CoV-2 |
|-------------------|---|---|--|
| Mouse | <ul style="list-style-type: none"> Popular model for acute lung injury Key differences from humans in anatomy and respiratory cell distribution Differences in physiological responses (no fever or sneezing or coughing) Not a model for transmission Many genetic tools: knockouts, reporters and other transgenics | <ul style="list-style-type: none"> Diverse viral strains that recapitulate spectrum of human disease, including acute respiratory distress syndrome Mouse adaptation not required for some IAVs, including avian viruses Many immunological tools to study host response | <ul style="list-style-type: none"> Mice require introduction of human ACE2 receptor (transgenic animal or viral transduction) for infection with unadapted virus Mouse-adapted SARS-CoV-2 does cause severe disease Together, diverse mouse models can recapitulate spectrum of disease in humans |
| Hamster | <ul style="list-style-type: none"> Small animal model of contact and airborne transmission for some viruses Limited genetic tools, but some genetic knockouts for key immune genes available | <ul style="list-style-type: none"> IAVs typically infect without adaptation Primarily upper respiratory tract infection with limited pathology Model for contact transmission and some evidence of airborne transmission Limited immunological tools to study host response | <ul style="list-style-type: none"> Unadapted SARS-CoV-2 infects hamsters Infection causes mild to moderate pathology in respiratory tract Some evidence that the model can recapitulate age- and sex-based differences in disease severity witnessed in humans Model for contact transmission and some evidence of airborne transmission |
| Ferret | <ul style="list-style-type: none"> Respiratory anatomy similar to humans Many respiratory viruses do not require adaptation for infection/pathogenesis Similarities in physiological responses (fever and sneezing) Model for transmission Outbred animals Few genetic tools | <ul style="list-style-type: none"> IAVs typically infect without adaptation (human and avian IAVs) Reporter viruses available to trace spread (fluorescent and luciferase-based) Limited immunological tools to study host response, but many are in development | <ul style="list-style-type: none"> Limited studies on SARS-CoV-2 transmission and pathogenesis thus far Unadapted SARS-CoV-2 infects ferrets Current models do not recapitulate severe disease in humans |
| Non-human primate | <ul style="list-style-type: none"> Respiratory anatomy most similar to humans Respiratory viruses do not require adaptation for infection or pathogenesis Similarities in physiological response (fever and respiratory distress) Outbred animals Few genetic tools Often serve as gatekeepers of vaccine candidates and therapeutics | <ul style="list-style-type: none"> IAVs infect without adaptation (human and avian viruses) Frequently used to study highly pathogenic IAVs Limited immunological tools to study host response | <ul style="list-style-type: none"> SARS-CoV-2 infects NHPs without adaptation of virus or manipulation of host Current models do not recapitulate severe disease in humans Clinical symptoms allow for testing efficacy of therapeutics NHPs exhibit adaptive immune responses to vaccination and infection |

ACE2, angiotensin-converting enzyme 2; IAV, influenza A virus; NHP, non-human primate; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Box 1 | Antiviral medications for influenza virus and SARS-CoV-2

Neuraminidase inhibitors (NAIs) were developed on the basis of rational drug design in the early 1990s²²⁴ and are influenza virus-specific antiviral medications. Oseltamivir, zanamivir, peramivir and laninamivir are available NAIs, each with different routes of administration. Of the NAIs, oseltamivir is the most studied and used. As their name suggests, these inhibit the function of viral neuraminidase (NA), which serves to limit viral progeny from being released from infected cells, thus reducing the number of cells subsequently infected. In adults with uncomplicated illness, oseltamivir has been shown to reduce the duration of symptomatic illness by ~24 h²²⁵. Although there are no randomized controlled trials of oseltamivir for the treatment of severe influenza virus infection, which may call into question the validity of the data²²⁶, observational studies have shown that oseltamivir has also been associated with a reduced risk of mortality in hospitalized adults with H3N2 seasonal influenza A virus (IAV)²²⁷ and the 2009 pandemic H1N1 IAV²²⁸, particularly when given early in hospital admission. Oseltamivir reduces the risk of death in patients hospitalized with highly pathogenic H5N1 IAV infection²²⁹. Resistance, conferred by the amino acid substitutions H275Y in N1 viruses or R292K in N2 viruses (among others), has been described²³⁰ and may emerge in high-risk groups on prolonged courses of NAI therapy²³¹.

Baloxavir is a newer influenza virus antiviral that inhibits the polymerase acidic (PA) cap-snatching endonuclease activity of the viral RNA-dependent RNA polymerase (RdRP) complex, halting viral replication. It has been shown to reduce the duration of symptoms by ~26 h after influenza virus infection and reduce viral load more quickly than oseltamivir²³². No resistance was reported in surveillance efforts in the United States²⁵, although resistance may emerge during treatment with baloxavir²³³.

Other antiviral compounds, including favipiravir, which inhibits viral RdRPs (not influenza virus specific and with some interest for potential treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2))²³⁰, and pimodivir, which inhibits influenza virus polymerase basic protein 2 (PB2)²³⁴, have activity against influenza virus and have been studied in human clinical trials, but are not currently widely available (favipiravir is approved in Japan for novel or emerging influenza viruses²³⁵). Finally, monoclonal antibodies targeting influenza virus haemagglutinin have been developed and tested in human clinical trials²³⁶; however, the role that these compounds have in influenza virus treatment strategies is currently unclear.

Remdesivir (GS-5734) is a RdRP inhibitor with in vivo activity against Ebola virus²³⁷, in vitro and in vivo activity against Middle East respiratory syndrome coronavirus (MERS-CoV)²³⁸, and in vitro activity against SARS-CoV-2 (REF.²³⁹). A large randomized clinical trial using time to recovery as a primary end point demonstrated the benefit of 10 days of remdesivir over placebo in adults hospitalized with lower respiratory tract infection due to SARS-CoV-2 (REF.²⁴⁰). The benefit was most evident if given early in disease and in patients requiring low-flow oxygen at enrolment²⁴⁰. Notably, however, a recent multinational WHO effort to study 'repurposed' antiviral medications (including remdesivir) to treat SARS-CoV-2 infection, which used in-hospital mortality as the primary end point, found no apparent benefit of 10 days of remdesivir therapy²⁴¹. Differences in treatment strategies, patient population and end points may account for variability in trial outcomes, and more study of remdesivir for SARS-CoV-2 infection may be necessary²⁴². As above, favipiravir for the treatment of human infection with SARS-CoV-2 is being studied²⁴³. As more is learnt about viral tropism, host response and in vivo replication, additional therapeutic targets throughout the viral life cycle will likely present themselves. Finally, monoclonal antibodies against the spike protein of SARS-CoV-2 have been developed and studied in clinical trials²⁴⁴.

by opportunistic bacteria. Mesenchymal cells are also primary producers of IL-6, which is consistently associated with severity^{94,219,220}. The IL-6 receptor antagonist tocilizumab is approved to treat chronic inflammatory diseases such as rheumatoid arthritis. Although it is unclear whether IL-6 is causal for influenza virus infection severity, as the cytokine has pleiotropic effects on the host response, there is continued interest in using tocilizumab to dampen excessive inflammation in severe respiratory infection, including influenza virus and SARS-CoV-2 infection^{97,221}, although a recent trial result did not show a benefit of a single dose of tocilizumab over usual care in adult patients hospitalized with COVID-19 (REF.²²²). As potent amplifiers of cytokine or chemokine production, endothelial cells represent an attractive target to reduce inflammation that is initiated in the respiratory tract. Several agonists of the S1P receptor have been developed to dampen inflammation and could potentially be used for numerous inflammatory diseases^{180,223}. None has yet been approved for respiratory viral infections, but their use in humans, including for COVID-19, has been proposed.

In contrast to targeting the mechanisms driving inflammation and disease resistance, an alternative approach could be to enhance directly the mechanisms of lung repair and disease tolerance. Preclinical studies in

animal models of severe IAV infection described above indicate that the growth factors GM-CSF, FGF10 and AREG all have the potential to enhance epithelial cell proliferation in vivo. An added benefit of directly promoting these repair mechanisms to promote recovery from severe infection is that it is possible that the antiviral, or more generally anti-pathogen, host response could be left intact to continue clearance of an ongoing infection or protect against a secondary bacterial infection.

The past decade of research on epithelial cells during lung injury has identified numerous pathways that could be manipulated with therapeutics, from early interferon responses and integrin signalling⁸⁹, to cell death mechanisms^{143–145}, to repair^{190,191,193}. A better understanding of how these pathways function in severe human infections is needed to identify the most promising targets to advance from preclinical studies. Moreover, it is unclear how these epithelial pathways might be dysregulated in high-risk groups, such as elderly individuals and individuals with obesity. The qualitative differences in epithelial repair from heterogeneous epithelial progenitor populations provide the opportunity to target specific pathways to influence the repair process and improve both short- and long-term outcomes.

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Author contributions

T.F., D.F.B. and V.M. researched data for the article. T.F., D.F.B., P.G.T. and S.S.C. contributed substantially to discussion of the content. All authors wrote the article. All authors reviewed and/or edited the manuscript before submission.

Competing interests

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