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Genetic influences on viral-induced cytokine responses in the lung

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Infection with respiratory viruses such as influenza, respiratory syncytial virus and coronavirus provides a difficult immunological challenge for the host, where a balance must be established between controlling viral replication and limiting damage to the delicate lung structure. Although the genetic architecture of host responses to respiratory viral infections is not yet understood, it is clear there is underlying heritability that influences pathogenesis. Immune control of virus replication is essential in respiratory infections, but overt activation can enhance inflammation and disease severity. Cytokines initiate antiviral immune responses but are implicated in viral pathogenesis. Here, we discuss how host genetic variation may influence cytokine responses to respiratory viral infections and, based on our current understanding of the role that cytokines play in viral pathogenesis, how this may influence disease severity. We also discuss how induced pluripotent stem cells may be utilised to probe the mechanistic implications of allelic variation in genes in virus-induced inflammatory responses. Ultimately, this could help to design better immune modulators, stratify high risk patients and tailor anti-inflammatory treatments, potentially expanding the ability to treat respiratory virus outbreaks in the future.

IMPACT OF INFLAMMATION ON PULMONARY VIRAL INFECTIONS

The primary role of the lung is gas exchange and oxygen delivery, which are fundamental processes for host survival, but also leave the lung vulnerable to pathogens due to constant exposure to the external environment.[1] Therefore, the lung provides a difficult immunological challenge for the host, where a balance must be maintained between defending against any would-be microbial invaders, whilst limiting damage to lung cells and the delicate structure. Infection with respiratory pathogens can lead to obstruction of the airways, loss of alveolar structure and degradation of the critical extracellular matrix; this damage can result in severely compromised lung function, potentially resulting in death of the host.[2,3]

To respond to respiratory pathogens, the host must initiate an immune response. Rapidly after infection, pathogen associated molecular patterns (PAMPs) are detected by pattern recognition receptors (PRRs), activating transcription factors (TFs), such as interferon regulatory factors (IRFs) and NFκB, which subsequently induce the upregulation of sets of genes including cytokines and interferons (IFNs). IFNs induce the upregulation of IFN-stimulated genes, ISGs, whose products can directly restrict pathogens. Cytokines and chemokines regulate the second arm of defence, recruiting and coordinating specific subsets of leucocytes. Increasing innate resistance to a pathogen and increasing tolerance to the resultant infection are two strategies of host defence; the severe lung inflammation associated with some respiratory infections is a difficult challenge for the immune system. Susceptibility occurs if a host is unable to reduce the pathogen burden or tolerate the negative consequences of the immune response.[4,5]

VIRAL RESPIRATORY PATHOGENS

The predominant viral pathogens causing lower respiratory tract infections (LRTI) in humans are respiratory syncytial virus (RSV), enteroviruses such as human rhinoviruses, adenoviruses, human metapneumovirus, influenza and parainfluenza viruses.[6] In addition, novel coronaviruses (CoVs) derived from animal populations have infected humans in recent years, including SARS-CoV-2, which also target the lower respiratory tract.[7] Furthermore, seasonal CoVs can cause acute LRTI in infants and immunocompromised patients.[8,9] Herein, we will briefly focus on the inflammatory responses induced by the more severe respiratory viral infections influenza, RSV and coronavirus, which are currently the respiratory viral pathogens that pose the most significant challenge to global public health.[10] We acknowledge the importance of bacterial co-infection, particularly with respect to influenza infection. However, due to space restrictions, we will focus on primary viral infections.

Influenza

Influenza is one of the most well-studied respiratory viruses. It occurs in two forms: seasonal (epidemic) influenza caused by Influenza A and B viruses (IAV), and sporadic pandemics caused by IAV.[11] In the majority of seasonal influenza infections, inflammation is usually limited to the upper respiratory tract, and symptoms are fairly mild.[12] However, during severe IAV infections, often associated with pandemic strains, the virus can reach the alveolar epithelium in the lower respiratory tract, potentially causing severe tissue damage, affecting gas exchange and sometimes leading to respiratory dysfunction or acute respiratory distress syndrome (ARDS).[13]

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In IAV-induced ARDS most of the lung pathology is associated with the release of cytokines and other pro-inflammatory mediators.[14] Elevated serum levels of pro-inflammatory cytokines and chemokines, including IL-1β, IL-6, TNF-α, IL-8, MCP-1, MIP-1β and IP-10, have been identified as markers of severity in acute lung injury during infection with IAV pandemic H1N1/09.[15–18] Furthermore, in humans, observations in H5N1-infected individuals suggest that high viral loads and the resulting intense inflammatory responses are central to influenza H5N1 pathogenesis, and that the focus of clinical management of this virus should consider preventing this intense cytokine response.[19] In young 'healthy' adults, IAV pH1N1/09 induces a TNF-α[hi] M1-like monocyte response that correlated with disease severity.[20]

In vivo models have been used to dissect roles for cytokines in IAV-associated pathogenesis. Despite the lack of susceptibility to many human IAV strains, mice are often used as an IAV model due to their practicality and versatility as an experimental system. Most research uses inbred C57BL/6 or BALB/C mice in conjunction with lab adapted A/Puerto Rico/8/1934 (H1N1) [PR/8] or A/WSN/1933 (H1N1) [WSN] influenza viruses. These tend to be more pathogenic in mice than humans; replicating and causing damage predominantly in the lower respiratory tract, causing rapid mortality, with severe lung inflammation associated with an influx of neutrophils and macrophages.[21] Highly pathogenic viruses of the H5N1 subtype, certain H7 subtype viruses and 2009 H1N1 pandemic strains do not need to be adapted for murine infection. X31, a reassortment virus with HA and NA genes of A/Hong Kong/1/1968 (H3N2) in the PR8 background, generates a milder infection in mice, and does not result in the rapid mortality observed with PR/8 and WSN.[22]

The type I IFNs, IFN-α and IFN-β, are expressed early in IAV infection and establish feedback loops through IFN α/β receptor signalling, sustaining the production of other pro-inflammatory cytokines such as IL-6, TNF-α and IL-1β.[23] Type I IFNs also induce factors that limit virus replication, such as members of the interferon-induced transmembrane (IFITM) and tripartite motif families.[24] Although type I IFN production is important for initiating antiviral responses, high type I IFN production during infection can drive exacerbated pathology by amplifying pro-inflammatory responses.[2] In studies using different mouse and IAV strains, there was a direct correlation between high IFNα/β levels and morbidity and mortality, linked to high levels of inflammatory cytokines and chemoattractants and subsequent pulmonary cellular inflammation, including increased inflammatory monocyte tumour necrosis factor-related apoptosis-inducing ligand expression and death receptor 5 expression on epithelia, mediating lung tissue damage.[25,26] In macaques, highly pathogenic avian influenza strain H5N1 induced sustained expression of innate, inflammatory and type I IFN genes, as well as complement pathway components, genes encoding antiviral proteins such as IFIT1 and IFIT2, and chemokines. This corresponded with apoptosis of DCs in the lung and the draining lymph node early in infection, and severe lung pathology. This was in contrast to infection with H1N1 strains, which induced less severe clinical disease in this model, where expression of type I IFN and inflammatory cytokines was initially high but dissipates rapidly,[27] in accordance with data from murine models demonstrating that sustained IFNα/β production induces pathology (28). In a similar macaque study, the severity of disease after infection with the 1918 pandemic strain of H1N1 influenza is also associated with severe pulmonary pathology, correlated with upregulation of inflammatory and cell death genes, with induction of macrophage and neutrophil infiltration resulting in acute lung inflammation and dysregulation of antiviral responses.[28] Type III IFNs (IFN-λs), also produced very early after infection, inhibit influenza spread from the upper respiratory tract to the lower respiratory tract in mice.[29] Murine models indicate that type III IFNs are important for controlling influenza replication in the lung mucosa, with IFNα/β-

signalling essential for controlling systemic immune responses. When mice are challenged with strains of IAV that can replicate outside the respiratory tract, Ifnar1^{−/−} and STAT1^{−/−} animals exhibit high viral titres in the liver, spleen and brain, in contrast to WT mice. However, with viruses that replicate solely with the respiratory tract, IFN-λ appears sufficient for viral control.[29,30]

Glucocorticoids, which suppress production of cytokines, are not protective in IAV infection in mice, suggesting that targeting the host inflammatory response may be ineffective.[31] Indeed, aside from data from dexamethasone treatment of COVID-19 (see below), little evidence from clinical studies suggests that glucocorticoids ameliorate symptoms of respiratory viral infections.[32,33] Importantly, however, cytokines such as IL-6 and TNF-α have pleiotropic roles in IAV infection; IL-6 is required for neutrophil survival in the lung[34] and antiviral T-cell development.[35] One study reported that TNF-α induces RIG-I expression, which enhances antiviral cytokine production,[36] and another demonstrated direct inhibition of viral replication in lung epithelial cells,[37] although both of these studies were carried out in vitro using cell lines. In vivo, TNF-α neutralisation ameliorates IAV-induced pulmonary inflammation and illness severity without impacting host control of IAV replication[38] and TNF-α deficient mice exhibit reduced IAV-induced lung pathology.[39] Triple mutant mice deficient in TNF-R1, TNF-R2 and IL-1-R1 display reduced lung inflammation and delayed onset of death when challenged with highly virulent H5N1 IAV (but not less virulent IAV), and this correlated with reduced pulmonary macrophage and neutrophil infiltrates.[40] IAV-induced TNF-α can induce monocyte migration.[41] TNF-α also exhibits pleiotropic functions from induction of cellular survival, proliferation and cellular suicide,[42] demonstrating a broad array of mechanisms through which TNF-α may drive IAV-induced lung damage.

Regulatory cytokines can dampen IAV-induced inflammation. For example, T cell-derived IL-10 ameliorates pulmonary inflammation, lethal lung injury and accelerated death, without impacting viral clearance,[43] although an antagonistic role for IL-10 in protective anti-IAV immunity has also been described.[44,45] The IL-12 family cytokine member IL-27 restricts IAV-induced weight loss, T_H1 and T_H17 cell, and neutrophil accumulation[46] and promotes the development of IAV-induced IL-10^{+} CD8 T cells.[47] IL-37, a member of the IL-1 family of ligands, acts as a negative feedback inhibitor of inflammatory cytokines, independently of anti-inflammatory cytokines such as IL-10.[48] Treatment of mice with IL-37 after influenza infection decreases lung injury and production of pro-inflammatory cytokines.[49]

Murine models of IAV infection have also revealed that myeloid cells can play both protective and immunopathogenic roles during IAV infection, with inflammatory monocytes and monocyte-derived DCs identified as driving inflammation and lung pathology,[50,51] with IAV-induced IFNs important in modulating homoeostatic versus inflammatory functions of monocytic cells.[52] In pathogenic IAV (PR8, H1N1) infection, partial amelioration of TNF-α-iNOS producing (Tip)-DC responses, which were elevated in lethal infections, exhibited protective activity, whereas complete ablation failed to ameliorate disease as tipDCs were essential for the development of protective CD8^{+} T-cell responses.[53] Modulation of inflammatory versus regulatory function of myeloid cells is important in determining outcome of IAV-associated disease. For example, CD200, expressed by lung epithelial cells, interacts with CD200R on alveolar macrophages (AMs), suppressing their inflammatory function and reducing amplitude and duration of inflammation post-IAV infection.[54]

RSV

RSV is an important aetiological agent of respiratory infections, particularly in children. Infections can be limited to the upper respiratory tract, but in cases associated with greater morbidity and mortality, RSV can cause LRTI, including pneumonia and

bronchiolitis.[55] Immune responses to RSV have been summarised in detail elsewhere, with age a major determinant in RSV-related disease.[56] Briefly, in some cases poorly controlled RSV replication occurs due to a delayed and/or ineffective immune response, resulting in a high viral load, and has been attributed to disease development. However, in other cases, an overexuberant immune response to the virus is observed, resulting in severe lung inflammation. As observed with IAV, levels of inflammatory cytokines such as IL-6 and TNF-α,[57–59] as well as chemoattractants such as CCL2,[60,61] which recruit inflammatory innate immune cells, have been found to be elevated in patients, correlating with disease severity, and are also induced after RSV-challenge in animal models. Increased cellular infiltrate comprising increased monocytes, T cells and neutrophils has been described in children with severe and fatal bronchiolitis.[62]

The balance of different T-cell subsets is known to correlate with different disease outcomes in RSV-infected infants. Initially, an imbalance in T_H1/T_H2 subsets was thought to explain some of the differences in clinical severity in RSV-infected individuals. However, more recently the balance between Treg and T_H17 subsets, and their roles in regulating T_H1/T_H2 skew and altering RSV disease pathogenesis, has begun to be elucidated.[63] Treg cells have been shown to play important anti-inflammatory roles during RSV infection via suppression of pathogenic activated $CD4^+$ and $CD8^+$ T cells and IL-13/GATA3-expressing T_H2-type $CD4^+$ T cells, inhibiting lung eosinophilia.[64] Furthermore, IL-10 production by Tregs dampens T-cell inflammation in the lung,[65] and therapeutic induction of Tregs reduces RSV-induced pulmonary inflammation without affecting viral clearance.[66] $\gamma\delta$ T cells promote RSV-induced inflammation and disease severity in mice[67] and these cells produce IL-17, which plays an important role in neutrophil recruitment and activation[68] and is increased in children with severe RSV. IL-33, a member of the IL-1 family of cytokines, acts as an alarmin at barrier sites, and can promote inflammatory diseases including allergic asthma, rheumatoid arthritis and chronic inflammation of the gut.[69] Age-dependent, rapid IL-33 production, which correlates with an increase in lung ILC2s, drives T_H2 biased RSV-induced immunopathogenesis.[70] Thus, alterations in cytokine profiles impacts RSV-associated disease outcome.[63]

As described for IAV, some cytokines play pleotropic roles in RSV infection. In a case report for two young children who died suddenly after contracting RSV, early IL-6 was elevated >200-fold above normal levels.[71] However, IL-6 has anti-inflammatory properties during RSV infection in a murine model via early induction of IL-27, which promotes regulatory T cell maturation and restricts T_H1-mediated immunopathology in this model,[72] and can suppress IL-17 production and associated mucous responses.[73] Type I IFN associates with severe RSV-associated lung inflammatory disease, amplifying pro-inflammatory cytokine production[74] and inducing recruitment of inflammatory monocytes to the lung, which can limit virus replication but, in excess, also contribute to damage.[75] AMs are also responsible for the recruitment and activation of NK cells after RSV infection,[76] with NK cells playing an important antiviral role, killing infected cells but also promoting T_H1 responses by production of IFN-γ.[77]

Coronaviruses
Newly emerging CoVs are becoming one of the greatest global health challenges of the twenty-first century. In the last 20 years, there have been three zoonotic outbreaks of beta-CoVs, causing a range of severe respiratory syndromes in humans. In 2002–2003, severe acute respiratory syndrome coronavirus (SARS-CoV) emerged from bat and palm civet populations and infected over 8000 people causing over 800 deaths; in 2012, Middle East respiratory syndrome coronavirus emerged from dromedary camel populations and is still endemic in the Middle East; and at the end of 2019, SARS-CoV-2 emerged from a currently unknown animal reservoir,[78] although it is thought to be of probable bat origin,[79] in

Wuhan, China, initiating a global pandemic resulting in hundreds of thousands of deaths at time of writing.

During the SARS-CoV outbreak, cytokine dysregulation was associated with disease severity in patients, and was accompanied by pronounced macrophage infiltration into lungs,[80] with T_H1-related cytokine storms observed in some severe clinical manifestations[81,82] accompanied by the accumulation of monocytes, macrophages and neutrophils.[82] Fatal SARS also associated with exacerbated IFN production and persistent expression of ISGs.[83] In a mouse model for SARS-CoV, pulmonary inflammation associated with complement-mediated lung disease,[84] and elevated chemokines and cytokines driven by inflammatory monocyte-macrophages resulted in vascular leakage, impaired virus-specific T cell responses, and ultimately reduced survival. This was demonstrated to be orchestrated by delayed type I IFN signalling. $Ifnar1^{-/-}$ mice were protected from lethal infection, interestingly without exhibiting increased viral load, suggesting that in SARS type I IFN drives immunopathology.[85] Conversely, in humans, the importance of the type I IFN pathway in protection against SARS-CoV-2 has been recently highlighted in a study demonstrating that individuals with loss-of-function variants in the TLR3- and IRF7-dependent type I IFN signalling pathway are pre-disposed to life-threatening pneumonia after infection with SARS-CoV-2.[86] Further highlighting the crucial role of type I IFN in COVID-19 immunity in humans, auto-antibodies against type I IFN, which were capable of neutralising the ability of type I IFNs to block SARS-CoV-2 infection in vitro, were associated with severe life-threatening COVID-19 infection.[87]

Symptoms in most SARS-CoV-2-infected patients are relatively mild to moderate, but in ~15% of patients there is progression to severe pneumonia, and about 5% eventually develop ARDS, septic shock and/or multiple organ failure.[88] The importance of inflammation in COVID-19 is highlighted by recent data demonstrating that dexamethasone, a corticosteroid, has been used in the randomised evaluation of COVID-19 therapy trial, reducing 28-day mortality among those receiving invasive mechanical ventilation or oxygen at randomisation.[89] Cytokines associated with secondary haemophagocytic lymphohistiocytosis, a hyperinflammatory syndrome characterised by fulminant and fatal hypercytokinaemia with multiorgan failure, have been found to be elevated in COVID-19 fatalities.[90] Indeed, high IL-6 and TNF-α,[91] and IL-6, IP-10 and IL-10[92] have been demonstrated to predict disease severity in clinical studies. Furthermore, in cell and animal models of SARS-CoV-2, in conjunction with transcriptional and serum profiling of COVID-19 patients, monocyte-associated chemokines such as CCL2 and CCL8 were shown to be elevated, along with neutrophil chemoattractants CXCL2 and CXCL8.[93] As elevated levels of circulating neutrophils have been observed among COVID-19 patients,[94,95] neutrophils may possibly contribute to disease severity. As observed in animal models of SARS-CoV, there was also delayed expression of type I IFN[93] although transcriptomics of BAL fluid from COVID-19 patients has revealed high ISG expression, together with chemokine-dominated hypercytokinemia.[96] In a mouse model of SARS-CoV-2, type I IFNs are significant drivers of pathological responses, enhancing expression of monocyte-recruiting chemokines and recruitment of pro-inflammatory cell types to the lung.[97] With no drugs or vaccines currently available for SARS-CoV-2, and the evidence from both SARS-CoV and SARS-CoV-2 patients that elevated cytokine expression correlates with pathology, there is increasing interest in the use of neutralising monoclonal antibodies targeting inflammatory cytokines and receptors. Tocilizumab, which targets the IL-6 receptor, has recently been used in a small clinical trial, where it was reported to reduce fever and improve respiratory function in 21 patients. Other potential targets considered include IL-1 and IL-17, as well as small-molecule inhibitors of signalling components downstream of these cytokines.[88]

INFLUENCE OF GENETIC VARIATION ON VIRAL-INDUCED INFLAMMATION

Substantial variation exists in individual outcomes following exposure to viral pathogens,[98] which in part will be influenced by microbial and environmental factors. Underlying risk factors including obesity, diabetes, chronic lung disease, cardiovascular disease, pregnancy, old or young age and being immunocompromised also alter disease susceptibility.[99] However, early familial studies indicated that deaths from infectious diseases had a strong genetic background.[100–102] Specifically for respiratory virus infections, there has been an increase in evidence of a genetic association between the host and the severity of influenza infection, with contribution of heritability to fatal outcome clear in some cases.[103] Furthermore, in the current SARS-CoV-2 outbreak, recent data from UK twin studies suggest that symptoms of COVID-19 may be heritable.[104]

Life-threatening primary infections often observed in childhood may more likely result from single-gene inborn errors of immunity.[105,106] Rare, loss-of-function mutations can result in life-threatening susceptibility to common infections and are due to deleterious variants in key genes of the immune system. The contribution of these monogenic disorders to infectious disease susceptibility has been reviewed elsewhere.[105–107] Identification of these mutations has exposed some of the underlying pathways essential for viral control in human hosts.[6,108] For example, it is well-characterised that loss-of-function mutations in the type I IFN pathway result in increased susceptibility to various viral infections,[109,110] although the detrimental effects of loss of type I IFN signalling can be compensated for by type II/III IFN in some cases.[111] Defective innate cytoplasmic recognition of RNA viruses, preventing activation of an efficient antiviral IFN response, can be caused by loss-of-function variants in *IFIH1*, leading to extreme susceptibility to common respiratory viruses.[6] Patients with deficiencies in IFN-γ responses, attributed to non-functional or dysfunctional IFN-γ receptors, have been shown to display increased susceptibility to viruses, including RSV and parainfluenza virus.[112] However, it is unlikely that these rare, highly penetrant, deleterious mutations contribute to the majority of infectious disease cases, because there is a lack of mendelian transmission in most cases of infectious disease susceptibility, and severe deleterious mutations should be rapidly eliminated from populations.[113]

Instead, severe infections in adults may result from a more complex combination of factors, with potential contribution of inherited (germline) genetic variation. The genetic architecture of infectious diseases is not yet fully understood. As described by Hill et al.,[113] it is possible that either: most genetic variation is encoded by relatively common genetic variants that cumulatively account for most of the genetic variance; that most relevant genetic variation is encoded by very rare mutations that have almost complete penetrance, as observed in primary immunodeficiency disorders; or that there is a predominant role for many individual rare variants with incomplete penetrance, with these three theories not necessarily being mutually exclusive. Dissecting the underlying mechanisms of variable susceptibility to respiratory viruses may help effective targeting of vaccine therapies, reveal new therapeutic approaches and, potentially, help contribute to future clinical risk prediction models.[114]

The introduction of genome-wide association studies (GWAS) revolutionised the field of complex disease genetics,[115] but very few GWAS studies have been performed for infectious diseases.[116] This is partly due to the very large sample sizes of cases and controls required from the same population, alongside well-characterised clinical data sets for each individual. Detection of specific genetic variants predisposing individuals to certain infectious diseases is more likely when these variants are polymorphic and have large effect sizes.[113] Therefore, most studies have relied upon candidate genetic variants based on

biological information pertaining to that specific genetic region, using targeted single nucleotide polymorphism (SNP)-genotyping in cases versus controls. As discussed above, disease severity after infection with respiratory viruses can correlate with increased expression of host inflammatory mediators, with evidence of decoupling of viral load and lung damage in some patients, suggesting that specific host predisposition could be responsible for the different magnitudes of inflammatory responses observed in patients.[20,56] Below, we review the host genetic susceptibility data available for increased susceptibility to respiratory viruses within the framework of inflammation as introduced in the first section of this review, with the current known genetic variants summarised in Fig. 1 and Table 1.

Cytokines and chemokines

Variants in genes encoding cytokines or chemokines, their receptors, or their promotor regions, have been associated with more severe infection outcomes for different respiratory viruses. In IAV infections, the most severe responses are associated with 'cytokine storms' or hypercytokinemia. As previously reviewed,[117] SNPs in *TNF*, *CCR5*, *IL1A* and *IL1B* are associated with susceptibility and severity of influenza infections, although the mechanism by which these SNPs may increase disease susceptibility remains to be fully elucidated. In accordance with possible anti-inflammatory functions of TNF-α, the *TNF* −238 *A* allele, which has been demonstrated to correlate with lower *TNF* transcripts, was overrepresented in IAV pH1N1/09 infected patients in comparison to healthy controls in a Caucasian population.[118] The T allele of rs17561 in *IL1A* is associated with a twofold increase in influenza infection risk, suggesting functional variation in the IL-1A protein in individuals with this genotype, although this has not been functionally validated.[119] *CCR5* encodes the receptor CCR5, which mediates leucocyte chemotaxis in response to ligands such as RANTES, MIP-1a and MIP-1b. Individuals who are heterozygotic for the *CCR5*-Δ32 mutation, which results in a 32 bp deletion in the coding region of the *CCR5* gene and partially reduced receptor expression,[120] exhibit more severe IAV disease,[121] although this was not replicated in subsequent studies in different populations.[122,123]

As reviewed by Kenney et al.[124] and Miyari and DeVincenzo,[125] there are several common human genetic variants associated with the development of a more severe RSV infection phenotype, including in genes encoding cytokines (*IL4*, *IL8*, *IL10* and *IL13*) and their receptors (*IL4RA*).[126–129] In a study in Korean children, the *IL4* common haplotype −589T was shown to be overrepresented in patients with severe disease. This SNP has been demonstrated to associate with increased transcriptional activity of *IL4*, suggesting that the increased T_H2 response observed in these patients could be mediated by *IL4* overexpression.[127] Similarly, an *IL8* haplotype comprising six SNPs (−251A/+396G/+781T/+1238delA/+1633T/+2767T) results in increased *IL8* transcripts in respiratory epithelial cells, with this haplotype shown to associate with the severity of RSV-induced bronchiolitis.[130] Despite the observation that very high levels of IL-6 can act as a biomarker for severe RSV in young children,[71] the IL-6 −174 *CC* genotype (low-production phenotype) is associated with a more severe illness after RSV infection.[131,132] In mice, early IL-6 production is required for IL-27 production by macrophages and monocytes, driving the local maturation of Tregs.[72] Haplotypes within the *IL13–IL4* locus have been associated with more severe RSV-related disease in infants.[127,133] IL-4 and IL-13 are two cytokines involved in the type II inflammatory response,[134] and excess T_H2 responses are observed in severe RSV disease.[133]

In accordance with a role for type I IFN in RSV pathogenesis in mice,[74,75] a SNP in *IFNA5* was strongly associated with the development of bronchiolitis, although the specific function of this SNP is currently undefined.[135] In a study genotyping children hospitalised with RSV infection, children who were heterozygous at position −592 (*CA*; rs1800872) in the *IL10* gene, which alters IL-
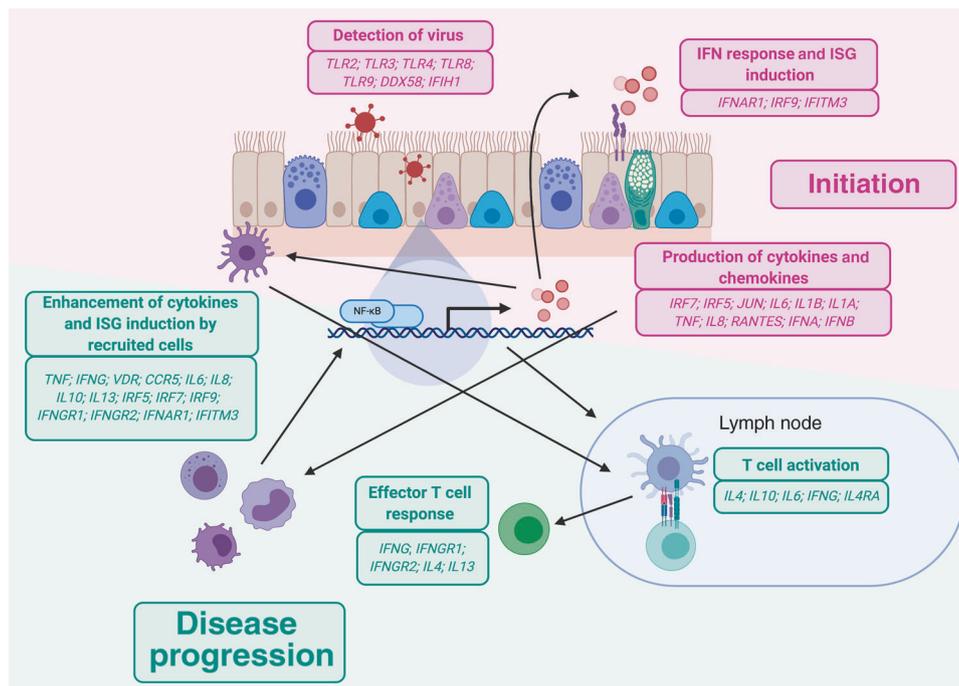
Fig. 1 Host genes with identified genetic variants associated with altered inflammatory phenotype post-infection with the respiratory viruses. Response to respiratory viruses requires initiation of an immune response. After viral infection of the lung epithelia, pathogen associated molecular patterns (PAMPs) are detected by host pattern recognition receptors (PRRs), such as TLRs and cytoplasmic sensors like RIG-I. This recognition starts a series of signalling cascades within the host cell, involving activation of TFs such as IRF5, IRF7 and AP-1, resulting in the production of pro-inflammatory cytokines such as IL-6, TNF and IL-1B, and type I IFNs. Cytokines produced by innate immune cells early post-infection drive several processes such as recruitment of circulating leucocytes, which, in turn, can enhance local cytokine production at the site of infection and enhance tissue damage; and activate dendritic cells to move to the lymph nodes and activate T cells by presentation of viral antigen on MHC molecules. Other innate immune cells such as macrophages and DCs also sense PAMPs through PRRs, again activating TFs and driving cytokine and IFN production. Acting through their receptors, type I IFNs establish an antiviral state in surrounding non-haematopoietic cells and recruited haematopoietic cells, where activation of TFs downstream of type I IFN receptors such as IRF9 results in the transcription of interferon stimulated genes (ISGs). The products of these ISGs play multifaceted roles: some can directly restrict processes such as viral replication and egress from the host cell, but some ISGs such as IFITM3 may also influence cytokine production in haematopoietic cells such as DCs. The cytokines produced early in infection also regulate the differentiation of T cells, with the balance between different T-cell subsets demonstrated to alter disease progression. Genes involved in these key processes, where specific genetic variants have been identified as associated with altering host inflammatory responses to IAV, RSV or SARS-CoVs, are shown. These genetic variants are further described in Table 1. Created with BioRender.com.

10 protein level,[136] were under-represented in the hospitalised group, suggesting that altered IL-10 mediated regulation of RSV-induced immune responses may alter outcome,[137] as implied by data from the murine models.[65] Moreover, genetic interactions between the IL-10 −592 and IL-4Rα −551 polymorphisms were observed in this human study, suggesting these alleles may interact, although the mechanism is currently unclear.[137]

There were few genetic susceptibility studies performed during the SARS-CoV 2003 outbreak, although in two Chinese cohorts from Hong Kong and Beijing, *RANTES* −28 G allele was associated with disease susceptibility and severity.[138] This genotype has previously been associated with enhanced promotor activity.[139] Interestingly, in a recent study in ten terminally ill, critical COVID-19 patients, blocking of CCR5, the receptor for RANTES, rapidly reduced plasma IL-6, restored CD4/CD8 T-cell ratios and significantly decreased SARS-CoV-2 viraemia, suggesting increased RANTES could contribute to SARS-CoV-2 disease severity by driving unchecked inflammation.[140]

Pattern recognition receptors (PRRs)
PRRs recognise viral PAMPs during respiratory viral infections and induce pro-inflammatory cytokines and IFNs.[141–143] Thus, genetic variation in PRRs and downstream signalling molecules that alter their abundance or activity may influence viral pathogenesis. Polymorphisms in *TLR3* associate with increased incidence of

influenza-related pneumonia in children infected with IAV pH1N1/09, specifically the rs5743313 *CT* genotype.[144] The *CC* genotype of this SNP was also associated with higher death outcomes in influenza-infected Chinese individuals. The exact mechanism of this SNP is undefined, however it is located in the intronic region of *TLR3* near exon 4, which is the region that encodes the transmembrane signal transduction domain, so it is potentially linked to impaired signalling and weakened host immune response.[145] The cytoplasmic sensor RIG-I, encoded by the gene *DDX58*, recognises dsRNA and 5′-triphosphates of the negative ssRNA IAV genome. Two heterozygous variants were identified in *DDX58* in a male Caucasian patient with severe IAV pH1N1/09 infection; SNP rs72710678 in the caspase activation and recruitment (CARD) domain and SNP rs138425677 in the RNA binding domain. These variants were associated with decreased recognition function of RIG-I, impaired antiviral responses and increased pro-inflammatory responses, corresponding with increased immunopathology.[146]

In infants hospitalised with RSV, disease severity associated with a p53-responsive *TLR8* SNP. After induction of p53 and incubation with single-stranded RNA ligands in human primary lymphocytes, SNP-dependent IL-6 expression, TLR8 expression and p53 binding were all increased.[147] Variation in *TLR4* also associates with severe RSV disease, although this has not been replicated in all cohorts.[56] Two SNPs encoding Asp299Gly and Thr399Ile substitutions in the

Table 1. Genetics variants contributing to respiratory disease.

Gene	Polymorphism	Effect on protein/function	Disease susceptibility virus association, and related host process presented in Fig. 1 (<u>initiation</u>/*disease progression*)
Cytokines, chemokines and receptors			
CCR5	CCR5-Δ32	32 bp deletion in *CCR5* coding region resulting in partially reduced receptor expression	↑Influenza A[121] *Enhancement of cytokines and ISG induction by recruited cells*
IL1A	rs17561 G > T Ser114Ala	Unknown	↑Influenza A[119] <u>Production of cytokines and chemokines</u>
IL1B	rs1143627 T > C	Possible increased *IL1B* expression associated with T allele; rs1143627 located on TATA box of *IL1B* promoter region, may affect TF binding	↑Influenza A[119] <u>Production of cytokines and chemokines</u>
TNF	rs361525 (*TNF* −238 A allele) G > A	Decreased *TNF* transcripts	↑Influenza A[118] <u>Production of cytokines and chemokines</u> *Enhancement of cytokines and ISG induction by recruited cells*
IL4	rs2243250 (*IL4* −589T allele) C > T	Increased *IL4* transcripts	↑RSV (embedded within common *IL4* haplotype defined at five loci)[127] *T-cell activation* *Effector T-cell response*
IL8	*IL8* haplotype: (−251A/+396G/+781T/ +1238delA/+1633T/ +2767T)	Increased *IL8* transcripts	↑RSV[130] <u>Production of cytokines and chemokines</u> *Enhancement of cytokines and ISG induction by recruited cells*
IL10	rs1800872 (−592 C/A allele) C > A	Currently not clear whether the C or A allele is associated with higher *IL10* expression	↓RSV with heterozygosity at this allele[137] ↑RSV −592 C allele in children ≤6 months of age[137] *Enhancement of cytokines and ISG induction by recruited cells* *T-cell activation*
IL13	rs1881457 (−1512 C allele) A > C rs1800925 (−1112 C/T allele) C > T	Unknown Altered expression of *IL13* and increased binding of nuclear factors to *IL13* promoter	↑RSV with −1512 C allele in the presence of allele 50 Ile in *IL4R* (rs1801275)[128] ↑RSV[128] *T-cell activation* *Effector T-cell response*
IL6	rs1800795 (−174 G/C allele) G > C	−174 CC low producer phenotype	↑RSV with CC allele[132] <u>Production of cytokines and chemokines</u> *Enhancement of cytokines and ISG induction by recruited cells* *T-cell activation*
IFNA5	rs10757212 C > T	Unknown	↑RSV[135] <u>Production of cytokines and chemokines</u>
RANTES	rs2280788 (−28 G allele) C > G	Possible enhanced promoter activity	↑SARS-CoV-1[138] <u>Production of cytokines and chemokines</u>
IFNGR1	201-2 A > G	Complete absence of IFN-γ responsiveness observed with homozygosity. Mutation in splice site at end of intron 2, in frame deletion of 34 amino acids, generating a truncated protein of assumed non-function.	↑RSV[112] *Enhancement of cytokines and ISG induction by recruited cells* *T-cell activation* *Effector T-cell response*
Pattern recognition receptors			
TLR3	rs5743313 T > C	Located in transmembrane signal transduction domain; potentially linked to reduced signalling	↑Influenza A with CC and CT genotypes[144,145] <u>Detection of virus</u>
DDX58	rs72710678 G > A Arg71His rs138425677 C > T Pro885Ser	CARD domain; decreased recognition function of RIG-I, impaired antiviral immune responses RNA binding domain; decreased recognition function of RIG-I, impaired antiviral immune responses	↑Influenza A[146] <u>Detection of virus</u>
TLR8	rs3761624 A > G	Located in *TLR8* promoter region. Increased *TLR8* mRNA expression following acute and chronic DNA damage stress in a p53RE SNP-dependent manner. Minor G allele creates a CWWG core in the second decamer of the p53RE within the *TLR8* promoter. The A allele in the rs3761624 variant disrupts the CWWG core, reducing p53 binding	↑RSV with G allele[148] <u>Detection of virus</u>

Table 1. continued

Gene	Polymorphism	Effect on protein/function	Disease susceptibility virus association, and related host process presented in Fig. 1 (initiation/*disease progression*)
TLR4	rs4986790 A > G/A > T Asp299Gly rs4986791 C > T	Located in ectodomain of *TLR4*; hyper-responsive LPS phenotype Located in ectodomain of *TLR4*; hyper-responsive LPS phenotype	↑RSV[148] Detection of virus
TLR2	rs1898830 C > A rs7656411 G > T	Intron variant Downstream variant 500 kB	↑Bronchiolitis[149] Detection of virus
TLR9	rs352162 C > T rs187084 C > T	Unknown Upstream variant 2 kB	↑Bronchiolitis[149] Detection of virus
IFIH1	rs35732034 C > T (IFIH1-Δ14) rs35337543 C > G (IFIH1-Δ8)	Minor allele T causes skipping of exon 14, resulting in a frame shift and an early stop codon in exon 15. IFIH1 protein lacks final 153 amino acids, including the C-terminal regulatory domain (CTD), essential for viral dsRNA binding Minor allele G causes skipping of exon 8, removing 39 amino acids at the end of the helicase 1 domain and in the linker part between helicase 1 and helicase 2 Severe disruption of IFIH1 signalling function, enzymatic activity, and protein stability in vitro demonstrated for both IFIH1-Δ8 and IFIH1-Δ14	↑RSV[8] Detection of virus
Transcription factors			
IRF7	Two compound heterozygous *IRF7* mutations—p.Phe410Val (F410V) and p.Gln421Q (Q421X)	F410V: missense substitution predicted to be damaging Q421X: nonsense mutation predicted to generate a premature stop codon Both alleles–lack of IRF7-dependent amplification of type I and III IFN post-influenza exposure	↑Influenza[153] Production of cytokines and chemokines *Enhancement of cytokines and ISG induction by recruited cells*
IRF9	991 G > A	Mutation in final nucleotide of exon 7 disrupts the essential splice site at the boundary of exon 7 and intron 7, resulting in mRNAs lacking exon 7 and an IRF9 protein probably lacking the IRF association domain (IAD), where STAT proteins bind. Cells with this mutation are impaired in ISG induction	↑Influenza[154] IFN response and ISG induction *Enhancement of cytokines and ISG induction by recruited cells*
JUN	rs11688 G > A	Unknown; synonymous variant	↑RSV[135] Production of cytokines and chemokines
VDR	rs10735810 (also rs2228570) C > T Thr1Met	Initiator codon variant, located at first start codon in exon 2, changes the translation initiation site, resulting in a truncated protein. Truncated protein may have higher activity than the wild type protein	↑RSV[135] *Enhancement of cytokines and ISG induction by recruited cells*
Viral restriction factors			
IFITM3	rs12252 T > C rs34481144 C > T	Unknown; synonymous variant Located in the promoter region of *IFITM3*, repression of *IFITM3* expression with A allele, possibly through enhanced CTCF binding to *IFITM3* promotor	↑Influenza[162,163,166] ↑SARS-CoV-2[163] ↑Influenza[161] IFN response and ISG induction *Enhancement of cytokines and ISG induction by recruited cells*

↑ = increased disease susceptibility/increased severity of symptoms; ↓ = decreased disease susceptibility/decreased severity of symptoms

TLR4 ectodomain, previously associated with TLR4 hypo-responsiveness to lipopolysaccharide (LPS), were represented at higher frequencies in children with symptomatic RSV disease.[148] Polymorphisms in *TLR2* and *TLR9* have been associated with more severe RSV-induced disease in children, although the mechanism of these SNPs has not been defined.[149] Thus, overall, SNPs associated with increased and decreased PRR functionality associate with severity of respiratory viral infections.

Transcription factors
Genetic variation in signalling molecules and TFs that act downstream of PRRs may also influence virus-induced inflammatory responses. Interferon regulatory factor 5 (IRF5) acts downstream of TLR7 and, possibly, RIG-I sensing of IAV to induce subsequent cytokine production.[150] In humans, multiple SNPs have been identified in the *IRF5* gene and regulatory regions, with some of these SNPs altering expression levels of IRF5,[151] implying that altered expression of TFs such as IRF5 could influence the magnitude of host inflammatory responses. As IRF5 has been implicated in other inflammatory conditions, such as systemic lupus erythematosus and inflammatory bowel disease, there is already interest in IRF5 as a therapeutic target in individuals with altered IRF5 expression.[152] IRF7 is known to act downstream of various PRRs, initiating transcription of type I IFN genes. Heterozygous null mutations in *IRF7* can lead to life-threatening IAV infection associated with significantly reduced type I and type

III IFN production and increased viral replication.[153] Polymorphisms in IRF7 have also been shown to alter the ability of plasmacytoid DCs to produce IFN-α in response to HIV-1, so it is not unreasonable to suggest these polymorphisms may also alter IFN responses to respiratory viral infections and associated pathogenesis. IRF9 is a key component of the ISG factor 3 trimer. In a child homozygous for a loss-of-function mutation *IRF9* allele hospitalised for severe pulmonary influenza, the child's cells were shown to be unable to respond fully or effectively to type I IFN, leading to a loss of viral control through the lack of ISG activation.[154] AP-1 combines with other TFs to activate transcription of cytokines and type I IFN. The rs11688 SNP in *JUN*, which encodes part of the AP-1 TF, associates with severe RSV-bronchiolitis.[135] In the same study, polymorphisms in vitamin D receptor (VDR) gene, demonstrated to increase the transcriptional activity of *VDR*, have been associated with the severity of RSV-induced bronchiolitis. VDR has been associated with down-regulating IL-12 and IFN-γ production.[149]

Viral restriction factors

Antiviral restriction factors constitute a first line of defence against viral entry to cells, blocking viral replication and propagation. *Mx1* is an ISG and encodes a potent viral restriction factor Mx1 in mice. Many inbred laboratory mice lack expression of a functional Mx1 protein, which explains enhanced susceptibility to influenza infection.[22,155] In human populations, there are allelic variants in *MX1*, and MXA, the GTPase encoded by *MX1*, has been demonstrated to restrict IAV.[156] However, none of these variants have been linked to influenza susceptibility currently.[157] There is increasing evidence that some viral restriction factors can also play additional, multifaceted roles, for example, acting as innate sensors and triggering innate immune responses.[158] One important viral restriction factor is the IFN-induced transmembrane protein 3 (IFITM3), which restricts cell entry of mainly enveloped RNA viruses including SARS-CoV and IAV.[159,160] Several SNPs have been identified in *IFITM3*, including rs34481144 within the promoter of IFITM3, with the minor allele (*A*) of this SNP associated with severity of IAV infection. The *A* allele of this SNP represses IFITM3 expression, possibly through enhanced binding of CTCF to the *IFITM3* promotor in this genotype.[161] The *CC* genotype of the rs12252 SNP, located in exon 1 of *IFITM3*, has been associated with severity of IAV infections by several groups.[162,163] This association was not observed in similar studies in European populations, where the frequency of the *CC* genotype is very low,[164,165] however, a recent meta-analysis confirmed the association between influenza susceptibility and rs12252.[166] As is likely the case with other risk alleles, cumulative effects have been observed for *TLR3* and *IFITM3* risk genotypes, suggesting a combination of genetic factors may influence host outcome post-influenza infection.[145] Additionally, the rs12252 *CC* genotype has been shown to be associated with more severe outcomes in SARS-CoV-2-infected Chinese patients, in an age-dependent manner.[167] The specific mechanism behind associations with the rs12252 SNP is currently unknown; initial predictions that the *CC* genotype would result in a truncated form of IFITM3 through alternative splicing have not been confirmed in subsequent studies.[168] More recently, IFITM3 has been shown to play roles asides from direct viral restriction. In a murine cytomegalovirus (MCMV) infection model, Ifitm3 acts to limit MCMV-related pathogenesis, independently of viral replication, by limiting the production of pro-inflammatory cytokines, particularly IL-6.[169] In humans, severe IAV disease in individuals with the *CC* genotype of the rs12252 SNP is associated with high CCL2 levels that drive pathogenic monocyte responses[20,163] and hypercytokinemia characterised by elevated levels of cytokines including IL-6 is associated with fatal H7N9 infection in individuals with the rs12252 *CC* genotype.[170]

INDUCED PLURIPOTENT STEM CELLS (IPSCS) AS TOOLS FOR STUDYING VIRAL INFLAMMATION

Investigation of respiratory viral infections has relied heavily on murine models and human cell lines, with important contributions of both of these systems to understanding disease pathogenesis. The mouse collaborative cross, a genetically diverse murine panel with up to eight functionally variant alleles at any given locus, generated to try to recapitulate human allelic diversity, provides a promising tool for addressing how genetic diversity can impact infection outcomes. In challenges with IAV, this model replicates human blood transcriptional responses to infection and has identified several quantitative trait loci contributing to specific host responses.[171,172] Human association studies that have identified polymorphisms in biologically plausible gene candidates provide some insights into molecular genetic contribution to pulmonary infections and disease severity; however, the function of these SNPs needs to be further dissected,[173] as statistical association studies do not provide mechanisms, making it difficult to establish causality between a candidate genotype and a clinical phenotype. Understanding these mechanisms requires detailed biochemical and immunological studies.[174] Findings from mouse models do not always translate to human disease, and most animal studies dissecting gene function have relied on full gene knockouts, which, whilst elucidating the role of that gene in response to pathogens such as influenza, do not provide information about differential responses associated with allelic variation.[175] Also, importantly, there is a greater level of redundancy in human immunity in comparison to inbred mouse lines, which means that phenotypes observed in mice are not always replicated in human studies.[106] For studying human cellular phenotype, the reductionist approach of using cell lines is often applied, but these cells lack some of the morphological characteristics of primary human cells, and do not allow the incorporation of human genotype. Therefore, there is a need for development of models enabling the study of causative mechanisms for effects of specific gene variants, which are currently lacking.[124]

Takahashi et al.[176] demonstrated that pluripotent stem cells could be generated from adult somatic cells by transduction with four TFs, providing an exciting opportunity for disease modelling in multiple cell and tissue types. iPSCs allow for the recapitulation of human 'disease in a dish' by facilitating the growth of unlimited quantities of a specific individual's cells and the differentiation of these cells down multiple cellular lineages.[177] Due to limited techniques to combine human genetics and the mechanisms of human cell biology, iPSCs fill a significant research gap, allowing for exploration of the effects of human genotype on cell phenotype.[178] Thus far, the use of iPSCs in facilitating host-viral research is still quite limited. However, some key studies have highlighted the potential of these systems to further dissect pathways regulating immune responses to viruses, and explore how differences in genetics may perturb these pathways.

In a study exploring genetic causes of severe influenza, heterozygous null mutations were identified in *IRF7* in a child suffering from life-threatening influenza. iPSCs generated from this patient and differentiated into pulmonary epithelial cells produced reduced type I IFN and allowed increased influenza virus replication.[153] Furthermore, patient-derived iPSCs were used to demonstrate that impaired TLR3- and UNC-93B-dependent IFN-α/β intrinsic immunity to HSV-1 in the CNS may underlie the pathogenesis of HSV-1 encephalitis in children with TLR3-pathway deficiencies.[179] We have also demonstrated the use of iPSC-derived dendritic cells (iPS-DCs) and iPSC-derived macrophages (iPSDMs) to investigate the role of IRF5 in regulating pro-inflammatory cytokine production after exposure of iPS-DCs and iPSDMs to IAV.[150]

Identification of more genetic variants that are associated with variations in viral-induced inflammatory responses will help to

determine novel gene associations that will advance the understanding of the molecular pathways involved in pathogenesis of specific viral diseases. Furthermore, in the last decade GWAS identified multiple genetic variants that contribute to various phenotypes; iPSCs are ideally placed to dissect how these variants contribute to the phenotypes described. With recently developed technologies such as CRISPR/Cas9, which allow for precision gene editing to generate, for example, isogenic control lines differing in just one SNP location,[180–182] the mechanistic implications of allelic variation in genes of interest can really begin to be probed. Furthermore, the development of large iPSC banks means that in the future experiments can be conducted on a population level scale.[178] iPSC technology opens up essential new avenues for exploring the contribution of genetics to infectious disease susceptibility, and may allow for better preparation in the future for emerging viral threats.

CONCLUSIONS

It is clear that inflammation plays a role in the pathology of various respiratory diseases. Modulating this inflammation as a therapeutic strategy remains challenging, as a delicate balance between protective immunity and excessive inflammation is a key. However, therapies targeting the host immune system are being trialled for different viral infections, and are attractive therapeutic prospects due to issues with increasing viral resistance to traditional antiviral therapies and the constant pressures on vaccine development due to emergence of novel viral strains in human populations. Furthermore, due to cross-over between the host pathways for viral-induced cytokine regulation for different viral pathogens, it is possible that host immunomodulatory therapies could be rapidly re-purposed in the advent of a pandemic. Therefore, enhanced understanding of these pathways, and how over-activation post-infection affects host survival, may be crucial.

Understanding the underlying genetics of specific individuals, which may alter that individual's propensity to experience overexuberant inflammatory responses after viral infection, could be very important for helping to design better immune modulators. Critically, such insight may be used to potentially stratify patients into high risk categories and tailor specific anti-inflammatory treatments based on understanding what immune responses are likely affected in these individuals. During the current COVID-19 pandemic, it is essential that we obtain as much information as possible regarding host factors that influence virus-induced inflammation, both to inform current clinical management of SARS-CoV-2 infection and to identify host genetic variants that, either in isolation or combination, alter inflammatory responses to other respiratory viral infections circulating in the human population presently, and in the future.

AUTHOR CONTRIBUTIONS

J.L.F. and I.R.H. contributed equally to the writing of this review.

ADDITIONAL INFORMATION

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