The role of interleukin-22 in lung health and its therapeutic potential for COVID-19

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Although numerous clinical trials have been implemented, an absolutely effective treatment against coronavirus disease 2019 (COVID-19) is still elusive. Interleukin-22 (IL-22) has attracted great interest over recent years, making it one of the best-studied cytokines of the interleukin-10 (IL-10) family. Unlike most interleukins, the major impact of IL-22 is exclusively on fibroblasts and epithelial cells due to the restricted expression of receptor. Numerous studies have suggested that IL-22 plays a crucial role in anti-viral infections through significantly ameliorating the immune cell-mediated inflammatory responses, and reducing tissue injury as well as further promoting epithelial repair and regeneration. Herein, we pay special attention to the role of IL-22 in the lungs. We summarize the latest progress in our understanding of IL-22 in lung health and disease and further discuss maneuvering this cytokine as potential immunotherapeutic strategy for the effective manage of COVID-19.

KEYWORDS
interleukin-22, immunotherapeutic strategy, lung, COVID-19, SARS-CoV-2 infection

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection has affected more than 548 million coronavirus disease 2019 (COVID-19) patients and caused more than 6.3 million deaths globally (https://coronavirus.jhu.edu, Johns Hopkins Coronavirus Resource Center) up to July 2, 2022, with these cases continuously increasing and producing several variants of concern. COVID-19 patients develop a constellation of clinical features, ranging from mild respiratory symptoms to severe acute respiratory syndromes, and even death (1, 2). Multiple evidences have illustrated that cytokine release syndrome (CRS) is the pathological hallmark of critically ill COVID-19 patients, which is characterized by a rapid and
sustained systemic increase of more than 20 inflammatory chemokines and cytokines. CRS induced secondary hemophagocytic lymphohistiocytosis and acute respiratory distress syndrome (ARDS) are regarded as main causes of organ injuries that drive the deterioration of COVID-19 (3–7). Therefore, besides direct supplemental oxygen and antiviral therapy for COVID-19 patients, immunotherapeutic strategies potentially alleviate COVID-19 progression and rescue severe or critical illness. Unfortunately, a recent double-blind, randomized Phase III trial (clinicaltrials.gov; NCT04320615) testing the treatment efficacy of an anti-interleukin (IL-6) receptor antibody (tocilizumab) in COVID-19 cases failed to show a significant reduced the mortality (8, 9). Thus, further studies aimed at exploration of novel immunomodulatory therapeutic strategies to treat COVID-19 and development corresponding regimens are urgently warranted.

Interleukin-22 (IL-22) has attracted great interest over recent years, making it one of the best-studied cytokines of the interleukin-10 (IL-10) family (10, 11). The function of IL-22 is mediated through directly interacting with its heterodimeric IL-22R1 and IL-10R2 receptor complex (12, 13). Unlike most interleukins, which directly regulate the function of hematopoietic cells, the major impact of IL-22 is exclusively on fibroblasts and epithelial cells due to the restricted expression of receptors in the kidney, lung, liver, pancreas, gastrointestinal tract, skin, and thymus (14). Therefore, IL-22 represents a main communication channel between specialized tissue cell types and the immune system. Signaling occurs via the activation of Jak1/Tyk2 and STAT3 pathway and then activation of anti-apoptotic, mitogenic and antioxidant molecules. Protein kinase B (AKT)/mechanistic target of rapamycin (mTOR), ERK1/2, P38, MAPK, STAT1, and STAT5 pathways are also activated by IL-22 (15–20). Of note, numerous of studies have illustrated that IL-22 plays a pivotal role in anti-viral infections through significantly ameliorating the immune cell-mediated inflammatory responses, as well as reducing lung injury and promoting further airway epithelial repair and regeneration (Figure 1) (21–23). Herein, we summarize recent progress in understanding the biology of IL-22 in lung health, suggesting more immunotherapeutic strategies to maneuver this cytokine for the effective manage of COVID-19 (24–28).

Pathological characteristics of COVID-19

COVID-19 is a complex disorder in which the respiratory performance is accompanied by systemic responses, illustrating viral infection generates widely dysfunctional immune reactions. Generally, the pathological feature of COVID-19 is bilateral diffuse alveolar damage with evidence of neutrophil extracellular traps, fibrin thrombi, and activated platelets in the vessels (25, 26). Infiltrating monocytes, macrophages, and neutrophils are clearly found in both lungs, accompanied by multinucleated syncytial cells infiltration in the alveoli that characterized by amphiphilic granular cytoplasm, large nuclei, and prominent nucleoli indicating viral cytopathic alters (27–31). Additionally, myocardial infarction, kidney damage, and persistent symptoms, such as depression, anxiety, palpitations, chest pain, sleep difficulty, dizziness, and weight loss, also represent the pathological features of critically COVID-19 cases (27–32). The immune profile in COVID-19 patients has been well reviewed, which shows dysfunction in both the innate and adaptive immune (33, 34). Specifically, CD16+ monocytes, γδ T cells, and NK cells are obviously activated, while the percentages of CD4+ T cells, CD8+ T cells, and natural killer (NK) cells are significantly decreased (34). Besides that, T cells show hyperinflammatory responses and enhanced migration abilities, along with evidence of expression of inhibitory molecules (7, 33, 34). The clonality of B cells and the proportion of plasma B cell compartments are also elevated. The percentages of dendritic cells are obviously decreased; however, the IFN-response cell compartments are increased (34–38). For the mechanisms, multiple evidence has demonstrated that IL-1 axis and IL-6 axis are the most importantly relevant signal transductions in the SARS-CoV-2-induced hyperinflammatory responses (39).

Altogether, the pathological characteristics of COVID-19 are complex, comprising fibrotic processes, hyperinflammation, thromboembolic complications and endothelial cells and lymphocyte dysfunction in the lung. These processes between patients are also highly variable, may be due to the heterogeneity of host immune reaction, which urgently require stratified and novel immunotherapy strategies for COVID-19 management.

Immunotherapeutic strategies for COVID-19

Despite numerous clinical trials have been implemented, an absolutely effective treatment against COVID-19 is still elusive. Immunomodulatory medications hold huge promise, but their administration should be cautiously considered so that the protective effects are appropriate for the dominant immunopathology and the disease stages to minimize the side-effects (Table 1).

Cytokine immunomodulators

Of note, immunotherapeutic strategies blocking proinflammatory cytokines or their receptors are only meaningful in the hyperinflammatory stages; as in the early stages of mild lung injury or minimal inflammation, cytokines are largely
desirable in fighting against virus infection. These include inhibitors of IL-1, IL-6, IL-18, TNF, CCR5 and GM-CSF or their receptors. However, some phase 2 or 3 results suggest no or little benefits in moderate and severe patients, and large-scale clinical data in COVID-19 are needed (8, 40–44, 54). Interferons (IFNs) have been used for many years to treat infectious disorders, cancers and multiple sclerosis, suggesting their potent antiviral effects for COVID-19. Although recent studies have found early nebulized IFN-α/β administration accelerated high-risk patients’ recovery and reduced mortality, the multinational clinical trials on hospitalized severe cases indicated subcutaneous IFNs injection with or without lopinavir treatment had minor effects on length of hospital stay and mortality (49, 50, 55, 56).

Kinase and inflammasome inhibitors

Small molecule inhibitors targeting cytokine-mediated signaling pathway, specifically of Janus kinases (JAKs), have also been well studied for treating COVID-19. For instance, Baricitinib and Tofacitinib were approved for emergency use authorization (EUA) because the clinical symptoms improved when co-treated with remdesivir during SARS-CoV-2 infection. But secondary infection and thromboembolism are the risk of these kinase inhibitors, which is highly dependent on administration time (45, 46). Glucocorticoids, such as dexamethasone, are broad-acting and powerful immunosuppressive and antiphlogistic therapies that can reduce mortality in critical COVID-19 cases (51). However, many clinical studies demonstrated that such efficacies are inevitably accompanied by multiple adverse effects, including viral reactivation, blocking of the host immune responses important for viral clearance, and others (51). In addition, it is indisputable that inflammasomes contribute to the pathogenesis of COVID-19, and trials on the GasderminD-pore inhibitor Disulfiram and the NLRP3 inhibitors Melatonin are ongoing (47, 48).

Neutralizing antibodies

Monoclonal antibody (mAb) is one of most effective immunotherapeutic strategies for the treatment of serious viral infection; thus, lots of mAbs are identified purposing to inhibit SARS-CoV-2 infection through binding to the spike protein. So far, the FDA has approved EUA for LY-CoV555 and Sotrovimab in pediatric and high-risk patients to prophylaxis and treat COVID-19, as these antibodies can reduce mortality and hospitalization (52, 57). Nevertheless, viral mutations present in variants/variants of concern (VOCs) have begun to gradually weaken the efficacies of many mAbs, and it is likely some will become invalid without upgrading to compensate for SARS-CoV-2 evolution (53). Altogether, immune system dysfunction plays a key role in COVID-19 pathogenesis and immunotherapeutic strategies for SARS-CoV-2 infection are promising, future efforts to discover more effective agents are obviously warranted. Also note that COVID-19 remains a field of rapid progress, thus recommendations on drugs and biomarkers will continue to evolve.
In the lung, stimulation of CD11b+-DCs and alveolar macrophages via their innate pattern recognition receptors leads to the secretion of related proinflammatory cytokines, expression of RORγt, differentiation of ILC3, γδT, Th17 and NKT cells, and production of IL-22 (57). Conversely, CD103+-DCs and plasmacytoid can be stimulated through viral antigens, resulting in the secretion of IL-27, IFN-γ and type I IFNs that block IL-22 expression in lymphocytes (58).

### Molecular mechanism

Multiple studies have shown that IL-22 is involved in lung repair, recovery and regeneration during lung infection or injury. From these studies, it is concluded that IL-22 can be protective or proinflammatory, where IL-22/IL-22R axis is important for host protective immunity to both viral infections and bacterial infections. The tissue protective nature of IL-22 via enhancing wound healing and the epithelial barrier through promoting antimicrobial peptides expression, enhancing anti-apoptosis and antiviral effects and alleviating airway inflammation, as well as inhibiting proinflammatory cytokines produced by airway epithelial cells (Figure 2). In contrast, the proinflammatory of IL-22 is evidenced by its ability to promote the expression of chemokines, and inflammatory cytokines such as IL-1β, IL-17, and TNF-α. Whether IL-22 has a protective or proinflammatory effect seems to depend on the related cytokines co-produced by the relevant cells during different stages of the diseases (10, 14).

### The regulation IL-22

Transcription factors play crucial roles in controlling the production of IL-22 in lungs (15, 59–61). Interestingly, studies indicate that these transcription factors, such as aryl...
hydrocarbon receptor (AhR), c-Maf, Batf, and Notch, can sometimes control IL-22 even in the same cells. These transcription factors form complex regulatory networks and regulate the production of IL-22 in context-dependent manners (62–64). As a cytosolic transcription factor, AhR is a harbor that converges several different environmental and cellular signaling to regulate the development of many T cell lines, including Tr1, Th17 and Treg cells via recognizing multiple natural molecules and small xenobiotics (62–65). AhR directly binds to cMaf and synergistically enhances IL-22 production in ILC3s, Th17 cells, γδ T cells and Th22 cells. Nevertheless, under some certain conditions, AhR may not produce IL-22, and AhR−/− mice can develop severe skin inflammation associated with higher IL-22 and IL-17 expression. The Notch signaling also promotes IL-22 expression via AhR induction in Th17 cells (65). Additionally, prostaglandin E2 (PGE2) enhances IL-22 production from both T cells and ILC3 via binding EP4 and EP2 receptors and blocking IRF-4, as well as activating AhR and cAMP signaling (66, 67) (Figure 3). In the lungs, certain viral or bacterial microorganisms can convert tryptophan (Trp) into derivatives that promote IL-22 secretion. Of importance, IL-22 production from γδ T cells is manipulated through AhR- and Try-dependent mechanism via CD69 (68). And CD69 regulates LAT-1 expression, which determines the intracellular quantity of AhR and the uptake of Trp (Figure 3). Moreover, both CARD−/− and IDO−/− mice can alter downstream Trp metabolites, for instance 3-IAID, with one depriving IL-22-promoting derivatives and the other favoring them, respectively (69). Taken together, these findings illustrate that controlling AhR signaling and Trp metabolites may be a powerful tool for regulating IL-22 functions.

### Protective effects of IL-22

During the early stage of influenza infection, studies has previously illustrated that IL-22 is overexpressed by NK and NKT cells in the lung, resulting in the airway and parenchymal epithelium regeneration. Within two days after viral infection, IL-22 gene transcription in γδ T, NKT and innate lymphoid cells is also increased in lung (Table 2). However, IL22BP gene transcription is decreased. During the sublethal stage of viral infection, IL-22 can inhibit lung inflammation, reduce secondary infection and preserve the integrity of lung epithelium (70). Whereas IL-22−/− mice infected with viral shows enhanced collagen accumulation and a defect in epithelial regeneration (70). Moreover, IL-22 can also prevent pulmonary fibrosis in a Bacillus subtilis induced model. Administration of IL-22 alleviates lung fibrosis, while inhibition of IL-22 leads to increased collagen accumulation in the lungs (71). In pneumococcal pneumonia, IL-22 gene is found to increase in the lung together with other cytokines, for example TNFα, IL-6, and IL-1. The absence of IL-22 makes the host vulnerable to pneumococcal infection, which indicates that the presence of IL22 is very important to control pneumococcal infection (72). IL-22 also plays a key role in host resistance to many other lung pathogens. During Klebsiella pneumonia infection, NK cells activation results in IL-22 production to protect lung tissue, and during infection with Streptococcus pneumoniae, TLR5 and DC cells activation leads to a repaid accumulation of ILC3s in the lungs to express IL-22 and defense against bacterial infection (73–75). During Chlamydia muridarum infection, IL-22 levels are rapidly increased in the lungs. Neutralization of IL-22 with anti-IL-22 mAbs can lead to impaired Th17 responses and deterioration of disease. Intranasal injection of IL-22 can

![Figure 2](image)

**Figure 2**
The role of IL-22 in lung health and diseases. In the lung, stimulation of mononuclear phagocyte via viral or bacterial pathogens leads to the secretion of related proinflammatory cytokines, then differentiation of ILC3, γδT, Th17 and NKT lymphocytes, and promoting or blocking of IL-22 expression. IL-22 can be protective or proinflammatory through multiple effects, where IL-22/II22R axis is important for host protective immunity to both viral infections and bacterial infections.
significantly enhance Th17 response and have a protective effect following Chlamydia pneumoniae infection (76). After Aspergillus fumigatus pulmonary infection, the fungal burden is increased in IL-22−/− mice, suggesting the critical role of IL-22 in the elimination of this pathogen (77). Additionally, IL-22 can also play a protective role in the barotrauma model, thereby reducing pulmonary edema and disintegration (78).

Proinflammatory effect of IL-22

In the animal model of bleomycin induced lung injury, it is demonstrated that IL-22 and IL-17 are predominantly produced by Th17 cells. Inhibiting IL-22 during bleomycin injection can improve airway inflammation, indicating IL-22 has a proinflammatory effect; nevertheless, airway inflammation is

TABLE 2  Immunotherapeutic strategies via targeting IL-22, in lung diseases.

| Diseases Type | IL-22 treatment | Observed effect |
|---------------|-----------------|-----------------|
| Influenza Viral | IL-22 deficient mice and recombinant IL-22 injection | Inhibits lung inflammation, reduce secondary infection and preserve the integrity of lung epithelium (59) |
| Bacillus subtilis infection Bacterial | Intratracheal treatment with recombinant IL-22 | Protection from lung fibrosis (60) |
| Pneumococcal pneumonia infection Bacterial | Systemically administration of recombinant IL-22 | IL22 is important for controlling pneumococcal infection (61) |
| Klebsiella pneumonia infection Bacterial | IL-22 neutralizing antibody and recombinant IL-22 injection | Defenses against bacterial infection (62, 64) |
| Streptococcus pneumoniae infection Bacterial | Endogenous IL-22 | Defenses against bacterial infection (63) |
| Chlamydia muridarum infection Chlamydia | IL-22 neutralizing antibody and intranasal injection | Significantly enhances Th17 response and has protective effects (65) |
| Aspergillus fumigatus pulmonary infection Fungal | IL-22 neutralizing antibody and IL-22 deficient mice | Lung defense against Aspergillus fumigatus is mediated by IL-22 production (66) |
| Ventilator-induced lung injury Tissue damage | Prophylactic inhalation of IL-22 | Alleviation of ventilator induced lung damage (67) |
| Bleomycin induced lung injury Tissue damage | IL-22 neutralizing antibody and recombinant IL-22 injection | Proinflammatory effect of IL-22 depends on the synergistic effect with IL-17 (68, 69) |
| Asthma models and asthmatic patients asthmatic | IL-22 neutralizing antibody and recombinant IL-22 injection | IL-22 induces the occurrence of asthma and ameliorates inflammation during asthma exacerbation (70–74) |
also significantly reduced in IL-17−/− mice with still high levels of IL-22 produced by T cells, suggesting IL-22 has a protective function for pulmonary fibrosis in deficiency of IL-17 (79, 80). Therefore, the proinflammatory effect of IL-22 may depend on the synergistic effect with IL-17 (Table 2).

Dual effects of IL-22 in asthma

In peripheral blood of asthmatic patients and preclinical asthma models, serum IL-22 levels are increased. The recent studies have indicated IL-22 can induce the occurrence of asthma in preclinical models, but it can ameliorate during asthma exacerbation (81, 82). In ovalbumin induced asthma animal model, IL-22 neutralization with mAbs during sensitization stage of disease, which is similar to the pulmonary fibrosis research just mentioned above, evidently alleviated lung pathology and airway inflammation. Subcutaneous administration of IL-22 during sensitization leads to worse lung pathology and inflammation (83–85). Conversely, IL-22 neutralization after sensitization can result in increased lung inflammation, whereas IL-22 injection decreases chemokine expression, goblet cell hyperplasia, production of IL-25, eosinophil infiltration and constriction of the airway (82–85). The mechanism behind this dual effect in allergic airway inflammation is unclear, but it may involve inhibiting the production of IL-25 and CCL17 through airway epithelial repair, which may involve IL-10.

In conclusion, IL-22 is involved in a variety of lung diseases, making it a promising target for clinical development.

Potential therapeutic effect of IL-22 for COVID-19

The emergence of SARS-CoV-2, which leads to COVID-19, is one of the most serious public health and epidemics crises in this century. As an emerging virus, there are multiple problems to be clarified in distinguishing the effective immune response of mild and severe diseases.

IL-22 in COVID-19 patients

Although IL-22 does not appear to reduce virus titer during infections, studies have illustrated that IL-22 can reduce the pneumonia severity via the immune regulation and tissue protective or regenerative functions (86, 87). As COVID-19 is a respiratory disorder with similar pathological characteristics and symptoms to other serious pulmonary virus infections, it is reasonable to speculate that IL-22 may also serve to limit the severity of this disease. More importantly, recent studies have shown that IL-22 has potent immune boosting, antiviral, and antibacterial properties to respiratory syncytial virus, which could also extend to manage SARS-CoV-2 infection (88). Accordingly, compared with healthy control individuals, the IL-22−/−Tc22 and IL-22−/−Th22 numbers in adult-COVID-19 patients increased significantly, whether it is asymptomatic pneumonia, mild pneumonia, or severe pneumonia (Figure 4). These findings further suggest that in the 0–12-year-old age group with asymptomatic disease course and uncomplicated adult cases, IL-22 expressed Tc22 cells are higher, which indicates that IL-22 has a protective effect (89). In contrast, the association between the increase of Tc17 cells and the severity of COVID-19 may reveal the destructive effect of co-expression of IL-17 and IL-22.

IL-22/IL-22R1 axis in COVID-19 patients

As the IL-22/IL-22R1 axis is involved in inflammation during virus infection, the expression patterns of IL-22/IL-22R1 on blood hematopoietic cells in SARS-CoV-2 infection have been well studied (90–93). The numbers of IL-22R1+ myeloid DC1, myeloid DC2, and plasmacytoid DC and the proportions of IL-22R1 intermediate, non-classical, and classical monocytes higher in COVID-19 patients than controls at the presented day. Moreover, high proportions of mDC2 and IL-22R1 non-classical monocytes show high HLA-DR expression and are therefore activated. Multivariate analysis is performed on all IL-22R1+ myeloid cells to distinguish the disease severity. However, correlation analysis between the concentration of plasma chemokines and IL-22R1+ cell subsets indicates that some subsets have protective effects, while others have pro-inflammatory effects (93, 94). Without stimulation, CD4+T and NK lymphocytes produced IL-22. CD4+T cells expressed IL-22R1, and its expression density defines two different functional subsets. The number of IL-22R1+ intermediate monocytes is negatively correlated with IFN-α, CRP and IL-6 in non-serious SARS-CoV-2 infection, whereas pDC and IL-22R1+ classical monocytes are positively correlated with pro-inflammatory chemokines IP-10 and MCP-1 in serious SARS-CoV-2 infections. Besides, researchers further demonstrate that IL-22 can reduce the expression of viral entry receptors, such as ACE2, TMPRSS2, and increase the expression of anti-viral proteins through IL-22/IL-22R1 pathway (Figure 4) (95). Thus, these findings suggest that the IL-22−/−IL-22R1 signaling is involved in the pathological process of COVID-19, which can be protective during SARS-CoV-2 infections (93–95).

ILC1s in COVID-19 patients

Recently, studies have demonstrated the roles of ILCs (innate lymphoid cells) in COVID-19 patients. Blood from severely infected COVID-19 patients were found that had fewer ILC precursor cells and ILCs than those mild cases. Of
importance, in these severely infected COVID-19 patients, the expression of CD69 in ILCs was higher, which as a marker for tissue homing and activation. ILCs-CD69+ increased and blood ILCs decreased in severe infections, indicating that severely infected COVID-19 patients have more lung homing and activation (96). Further findings corroborate these results by confirming that higher ILCs abundance in blood was associated with shorter hospitalization. Additionally, the number of ILCs in the blood of hospitalized patients with SARS-CoV-2 infection decreased by 1.8 times (97). Collectively, these studies demonstrate that there are correlations between severe COVID-19 and decreased ILCs in the blood. As IL-22 plays critical functions in epithelial barrier integrity and ILCs are identified as the major source of IL-22 in response to lung pathogens stimulation (98), further studies are urgently needed to assess their exact roles in SARS-CoV-2 infection since current results regarding IL-22 and ILCs in COVID-19 individuals are obtained via analysis of blood periphery (Figure 4).

Concerns of Interleukin-22 application

Although IL-22 possesses definite immunomodulatory properties and tissue-protective effects, mainly via inhibiting apoptosis and promoting proliferation of epithelial cells, these same effects have also been involved in pathological states such as psoriasis, rheumatoid arthritis, and malignant tumors (99, 100). Additionally, functions of IL-22 have been implicated in host defense within barrier-tissues such as the skin, oral mucosa, and intestine (100–102). The functional outcomes of IL-22 in immunomodulation may be either protective or pathologic, suggesting that it is an extremely controversial interleukin (96–98). Systemic administration of IL-22 can upregulate the expression of proinflammatory cytokines including G-CSF and IL-6, and chemokines like chemokine (C-X-C motif) ligands CXCL1, CXCL5, CXCL9, which is sufficient to cause an inflammatory response (99). Studies indicate that IL-22 serum levels in psoriasis and rheumatoid arthritis patients are much higher than that the health individuals, and these also correlate with the disease severity (103, 104). Of note, IL-22−/− mice significantly alleviate collagen induced arthritis (105). In rheumatoid arthritis tissues, synovial fibroblasts are considered to be the key cellular target of IL-22, which may drive the proliferation of this cell type through STAT3 (106). Besides, synovial-fibroblasts activation via IL-22 can upregulate the expression of NF-KB ligand and CCL2, which promote inflammation and joint destruction (106, 107). Inhibition of IL-22 biological activity can also reduce the severity of psoriasis, which is also consistent with the psoriasis like symptoms in IL-22 transgenic mice (108–110). Keratinocytes are targets of IL-22 in psoriasis, and IL-22 regulates the expression of key inflammatory parameters by keratinocytes, including matrix metalloproteinases-1, IL-20 and CXCL5 (108–111). It is worth mentioning that studies have also suggested that IL-22 may also promote lung pathology during chronic exposure to Aspergillus fumigatus (112). As overactivation of STAT3 in a variety of human tumors, IL-22 is considered to be associated with many...
Conclusions and future perspectives

In summary, it can be concluded that IL-22 is a crucial modulator of epithelial homeostasis and a regulator of host defense in the lung. It provides communication channels that allow hematopoietic cells, especially lymphocytes, to trigger pleiotropic responses in the epithelium to maintain barrier homeostasis against pulmonary pathogens while protecting the lungs from invasion or damage. IL-22 participates in various lung diseases through epithelial protection or regeneration, making it an extremely attractive cytokine for the treatment of COVID-19. Of note, the FDA has approved several research groups to study the efficacy of IL-22 during SARS-CoV-2 infection (116–118). These clinical trials suggest that IL-22 treatment can shorten the duration of Intensive Care Unit (ICU) stay. Therefore, it is necessary to further comprehensively understand the specific mechanisms and functions of IL-22 in regulating the lung microenvironment, which could enable to identify novel immunotherapeutic strategy for COVID-19. However, IL-22 has been demonstrated to promote tumor growth and accelerate inflammation in a few animal models. The therapeutic consequences of IL-22 in either direction for COVID-19 treatment should be evaluated, which will provide useful insights into its role in lung health.

Author contributions

WC and SF wrote the manuscript. WC, YL and DJ designed the structures and supervised the work. The final version of this paper has been approved by all authors.

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Conflict of interest

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References

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in wuhan. China Lancet (2020) 395:497–506. doi: 10.1016/S0140-6736(20)30183-5
2. Vabret N, Britton GJ, Gruber C, Hegde S, Kim J, Kukin M, et al. Immunology of COVID-19: current state of the science. Immunity (2020) 52:910–41. doi: 10.1016/j.immuni.2020.05.002
3. Wong LR, Perlman S. Immune dysregulation and immunopathology induced by SARS-CoV-2 and related coronaviruses - are we our own worst enemy? Nat Rev Immunol Nov (2021) 22:47–56. doi: 10.1038/s41577-021-00656-6
4. Li J, Lai S, Gao GF, Shi. The emergence W. Genomic diversity and global spread of SARS-CoV-2. Nature (2021) 506:497–506. doi: 10.1038/s41586-021-04188-6
5. Mathew D, Giles JR, Baxter AE, Oldridge DA, Greenplate AR, Wu JE, et al. Deep immune profiling of COVID-19 patients reveals distinct immunotypes with therapeutic implications. Science (2020) 369:eaab5851. doi: 10.1126/science.abc5851
6. Kuri-Cervantes L, Lampaena MB, Meng W, Rosenfeld AM, Ittmier CA, Weisman AR, et al. Comprehensive mapping of immune perturbations associated with severe COVID-19. Sci Immunol (2020) 5:eabd7114. doi: 10.1126/sci Immunol.5ab7114
7. Song J, Zhang C, Fan X, Meng F, Xu Z, Xia P, et al. Immunological and inflammatory profiles in mild and severe cases of COVID-19. Nat Commun (2020) 11:3410. doi: 10.1038/s41467-020-17240-2
8. Salama C, Chan J, Yau L, Reiss WG, Kramer B, Neidhart JD, et al. Tocilizumab in patients hospitalized with covid-19 pneumonia. N Engl J Med (2021) 384:20–30. doi: 10.1056/NEJMoa2030340
9. Brown MJ, Alazawi W, Kanoni S. Interleukin-6 receptor antagonists in critically ill patients with COVID-19. N Engl J Med (2021) 384:1491–502. doi: 10.1056/NEJMoa2104842
10. Sabat R, Ouyang W, Wolk K. Therapeutic opportunities of the IL-22-IL-22R1 system. Nat Rev Drug Discovery (2014) 13:21–38. doi: 10.1038/nrd4176
11. Dumoutier L, Louahed J, Renaud AJ. Cloning and characterization of IL-10-related T cell-derived inducible factor (IL-TIF), a novel cytokine structurally related to IL-10 and inducible by IL-9. J Immunol (2000) 164:1814–9. doi: 10.4049/immunol.164.4.1814
12. Xie MH, Aggarwal S, Ho WH, Foster J, Zhang Z, Stinson J, et al. Interleukin (IL)-22, a novel human cytokine that signals through the interferon receptor-related proteins CRF2-4 and IL-22R. J Biol Chem (2000) 275:31335–9. doi: 10.1074/jbc.M000534200
13. Kotenko SV, Izotova LS, Mirochnitchenko OV, Estrova E, Dickensheets H, Donnelly RP, et al. Identification of the functional interleukin-22 (IL-22) receptor complex: the IL-10R2 chain (IL-10R) is a common chain of both the IL-10 and IL-22 (IL-10-related T cell-derived inducible factor, IL-TIF) receptor complexes. J Biol Chem (2001) 276:2725–32. doi: 10.1074/jbc.M007873200
infection in noshuman primates. Sci Transl Med (2021) 13.eafl1906. doi: 10.1126/scitranslmed.afl1906.

58. Dudakov JA, Hanash AM, van den Brink MR. Interleukin-22: immunobiology and pathology. Annu Rev Immunol (2015) 33:747–85. doi: 10.1146/annurev-immunol-031914-121123.

59. Aphetel L, Quintana FJ, Pot C, Joller N, Xiao S, Kumar D, et al. The aryl hydrocarbon receptor interacts with c-myc to promote the differentiation of type I regulatory T cells. J Immunol (2010) 185:845–51. doi: 10.1074/jimmunol.100879.

60. Gandhi R, Kumar D, Burns EJ, Nadeau M, Duke L, Laroni A, et al. Activation of the aryl hydrocarbon receptor induces human type 1 regulatory T cell-like and Foxp3(+) regulatory T cells. Nat Immunol (2010) 11:846–53. doi: 10.1038/nmi.2011.38.

61. Quintana FJ, Basso AS, Iglesias AH, Korn T, Farez MF, Bettelli E, et al. Control of treg and Th(17) cell differentiation by the aryl hydrocarbon receptor. Nature (2008) 453:65–71. doi: 10.1038/nature06808.

62. Qiu J, Guo X, Chen ZM, He J, Sonnenberg GF, Kirn TJ, Zaph C, Fouser LA, Artis D. Pathological versus protective functions of IL-22 in airway inflammation are regulated by IL-17A. J Exp Med (2010) 207:1293–305. doi: 10.1084/jem.20092054.

63. Guo P, Wang D, Zhang J, Wang X, Chen Z, Gu L, et al. Protective function of interleukin-22 in pulmonary fibrosis. Clin Transl Med (2021) 11:e1609. doi: 10.1186/s13287-021-01609-9.

64. Farfariello V, Amanti C, Nabi I, Morelli MB, Aperio C, Capussotti S, et al. IL-22 mRNA in peripheral blood mononuclear cells from allergic rhinitic and asthmatic pediatric patients. Pediatr Allergy Immunol (2011) 22:419–23. doi: 10.1111/j.1399-3038.2010.01166.x.

65. Besnard AG, Sabat R, Dumoutier L, Renaud J, Willart M, Lambrecht B, et al. Dual role of IL-22 in allergic airway inflammation and its cross-talk with IL-17A, am. J Respir Crit Care Med (2011) 183:1153–63. doi: 10.1164/rccm.201008-1385OC.

66. Akagome K, Inamura M, Kawaihata K, Harada H, Okumitsu K, Matsumoto T, et al. High expression of IL-22 suppresses antigen-induced immune responses and eosinophilic airway inflammation via an IL-10-associated mechanism. J Allergy Clin Immunol (2011) 128:1067–76. doi: 10.1016/j.jaci.2011.06.018.

67. Badi YE, Pavlo AB, Pavlova S, Riley JH, Bates S, Kermani NZ, et al. Mapping atopic dermatitis and anti-IL-22 response signatures to type 2 low-severity neutrophilic asthma. J Allergy Clin Immunol (2022) 149:89–91. doi: 10.1016/j.jaci.2021.04.041.

68. Pociask DA, Scheller EV, Mandalapu S, McHugh KJ, Endow RL, Fattman CL, et al. IL-22 is essential for lung epithelial repair following influenza infection. Am J Pathol (2013) 182:1286–96. doi: 10.1016/j.ajpath.2012.12.007.

69. Kumar P, Thakar MS, Ouyang W, Malarkannan S. IL-22 from conventional nK cells is epithelial regenerative and inflammation protective during influenza infection. Microsc Immunol (2013) 6:69–82. doi: 10.3388/mi.2012.49.

70. Das S, Croix CS, Good M, Chen J, Zhao J, Hu S, et al. Interleukin-22 inhibits respiratory syncytial virus production by blocking virus-mediated subversion of cellular autophagy. Sci Transl Med (2020) 23:101256. doi: 10.1126/scitranslmed.aaz7877.

71. Cagan E, Teczkan G, Simsek A, Kiemetz MA, Dombaz F, Asan A, et al. The age-dependent role of Th22, Th22c, and t17 cells in the severity of pneumonia in covid-19 immunopathogenesis. Viral Immunol (2022) 35:318–27. doi: 10.1089/ vimi.2021.0213.

72. Hebert KD, McLaughlin N, Zhang Z, Cipriani A, Alcorn JF, Pociask DA. IL-22 is induced during influenza infection by direct and indirect TLR9 induction of STAT1. Respir Res (2019) 20:184. doi: 10.1186/s12931-019-1153-4.

73. Brias SG, Stack G, Stacey MA, Redwood AJ, Humphreys IR. The role of IL-22 in viral infections: paradigms and paradoxes. Front Immunol (2016) 7:211. doi: 10.3389/fimmu.2016.00211.

74. Zenevics LA, IL-22: there is a gap in our knowledge. ImmunoHorizons (2018) 2:198–207. doi: 10.4049/immunohorizons.1800006.

75. Albarayn N, Cano CO, Karimi S, Dogahae D, Praet AV, Godfried A, et al. Distinct expression patterns of interleukin-22 receptor 1 on blood hematopoietic cells in SARS-CoV-2 infection. Front Immunol (2022) 13:769839. doi: 10.3389/fimmu.2022.769839.

76. Savan R, McFarland AP, Reynolds DA, Feigenbaum L, Ramakrishnan K, Carmon W, et al. Novel role for IL-22 as a driver of inflammation. Blood (2011) 117:575–94. doi: 10.1182/blood-2010-05-285908.

77. Klooster JPT, Bol-Schoenmakers M, van Summeren K, van Vliet ALW, de Wit M, Kokkinou E, Garcia JC, Parrott T, Palma Medina LM, Maleki KT, et al. Innate lymphoid cell composition associates with covid-19 disease severity. Clin Transl Immunol (2020) 9:e1224. doi: 10.1089/cit.2020.1224.

78. Angen JA, Vlachos N, Green KS, Kofler M, Slevin E, Pocock S, et al. Protective properties of inhaled IL-22 in a model of ventilator-induced lung injury. Am J Respir Cell Mol Biol (2011) 44:369–76. doi: 10.1165/rcmb.2009-0440OC.

79. Sonnenberg GF, Nair MG, Kirn TJ, Zaph C, Fouser LA, Artis D. Protective properties of type 1 IL-22 in a model of ventilator-induced lung injury. Am J Respir Cell Mol Biol (2011) 44:369–76. doi: 10.1165/rcmb.2009-0440OC.

80. Pociask DA, Scheller EV, Mandalapu S, McHugh KJ, Endow RL, Fattman CL, et al. IL-22 is essential for lung epithelial repair following influenza infection. Am J Pathol (2013) 182:1286–96. doi: 10.1016/j.ajpath.2012.12.007.

81. Cagan E, Teczkan G, Simcek A, Kiemetz MA, Dombaz F, Asan A, et al. The age-dependent role of Th22, Th22c, and t17 cells in the severity of pneumonia in covid-19 immunopathogenesis. Viral Immunol (2022) 35:318–27. doi: 10.1098/ vimi.2021.0213.
99. Sonnenberg GF, Fouser LA, Artis D. Border patrol: regulation of immunity, inflammation and tissue homeostasis at barrier surfaces by IL-22. *Nat Immunol* (2011) 12:383–90. doi: 10.1038/ni.2025

100. Sonnenberg GF, Fouser LA, Artis D. Functional biology of the IL-22-IL-22R pathway in regulating immunity and inflammation at barrier surfaces. *Adv Immunol* (2010) 107:1–29. doi: 10.1016/B978-0-12-381300-8.00001-0

101. Fabre T, Molina MF, Souchy G, Goulet JP, Willerms B, Villeneuve JP, et al. Type 3 cytokines IL-17A and IL-22 drive TGF-beta-dependent liver fibrosis. *Sci Immunol* (2018) 3 eaar7754. doi: 10.1126/sciimmunol.aar7754

102. Powell N, Pantazi E, Pavlidis P, Tsakmaki A, Li K, Yang F, et al. Interleukin-22 orchestrates a pathological endoplasmic reticulum stress transcriptional programme in colonic epithelial cells. *Gut* (2020) 69:578–90. doi: 10.1136/gutjnl-2019-318483

103. Nakajima H, Nakajima K, Tarutani M, Morishige R, Sano S. Kinetics of circulating Th17 cytokines and adipokines in psoriasis patients. *Arch Dermatol Res* (2011) 303:451–5. doi: 10.1007/s00403-011-1159-3

104. Leipe J, Schramm MA, Grunke M, Baeuerle M, Dechant C, Nigg AP, et al. Interleukin 22 serum levels are associated with radiographic progression in rheumatoid arthritis. *Ann Rheum Dis* (2011) 70:1453–7. doi: 10.1136/ard.2011.152074

105. Geboes L, Dumoutier L, Kelchtermans H, Schurgers E, Mitera T, Renauld JC, et al. Proinflammatory role of the Th17 cytokine interleukin-22 in collagen-induced arthritis in C57BL/6 mice. *Arthritis Rheumatol* (2009) 60:390–5. doi: 10.1002/art.24220

106. Ikeyashi H, Kurowsa T, Hirama T, Nakazato Y, Kano K, Kuma K, et al. Expression of interleukin-22 in rheumatoid arthritis potential role as a proinflammatory cytokine. *Arthritis Rheumatol* (2005) 52:1037–46. doi: 10.1002/art.20965

107. Kim KW, Kim HR, Park JY, Park JS, Oh HJ, Woo YJ, et al. Interleukin-22 promotes osteoclastogenesis in rheumatoid arthritis through induction of RANKL in human synovial fibroblasts. *Arthritis Rheumatol* (2012) 64:1015–23. doi: 10.1002/art.33446

108. Van Belle AB, de Heusch M, Lemaire MM, Hendrickx E, Warnier G, Dumont AS, et al. IL-22 is required for imiquimod-induced psoriasiform skin inflammation in mice. *J Immunol* (2012) 188:462–9. doi: 10.4049/jimmunol.1102224

109. Park O, Wang H, Yoon H, Feigenbaum L, Li H, Yin S, et al. In vivo consequences of liver-specific interleukin-22 expression in mice: implications for human liver disease progression. *Hepatology* (2011) 54:252–61. doi: 10.1002/hep.24339

110. Li C, Xu M, Coyne J J, Wang W, Davila ML, Wang Y, et al. Psoriasis-associated impairment of CCL27/CCR10-derived regulation leads to IL-17A/IL-22-producing skin T-cell overactivation. *J Allergy Clin Immunol* (2021) 147:759–63. doi: 10.1016/j.jaci.2020.03.044

111. Bellone M, Brevi A, Huber S. Microbiota-propelled T helper 17 cells in inflammatory diseases and cancer. *Microbiol Mol Biol Rev* (2020) 84:e00064-19. doi: 10.1128/MMBR.00064-19

112. Lilly LM, Gessner MA, Dunaway CW, Metz AE, Schwiebert L, Weaver CT, et al. The β-glucan receptor dectin-1 promotes lung immunopathology during fungal allergy via IL-22. *J Immunol* (2012) 189:3653–60. doi: 10.4049/jimmunol.1201797

113. Johnston PA, Grandis JR. STAT3 signaling: anticancer strategies and challenges. *Mol Interv* (2011) 11:18–26. doi: 10.1124/mi.11.1.4

114. Thilakasiri PS, Dmello RS, Nero TL, Parker MW, Ernst M, Chand AL. Repurposing of drugs as STAT3 inhibitors for cancer therapy. *Semin Cancer Biol* (2021) 68:31–46. doi: 10.1016/j.semcancer.2019.09.022

115. Jiang R, Tan Z, Deng L, Chen Y, Xia Y, Gao Y, et al. Interleukin-22 promotes human hepatocellular carcinoma by activation of STAT3. *Hepatology* (2011) 54:906–9. doi: 10.1002/hep.24486

116. ClinicalTrials.gov. A study to evaluate the safety and efficacy of mstt1041a (astegolimab) or uttr1147a in patients with severe covid-19 pneumonia (covastil) (2020). Available at: https://clinicaltrials.gov/ct2/show/NCT04386616.

117. ClinicalTrials.gov. Study of f-652 (il-22: igg2 fusion protein) in patients with moderate to severe COVID-19 (2020). Available at: https://clinicaltrials.gov/ct2/show/NCT04498377.

118. McAleer JP, Kolls JK. Directing traf: IL-17 and IL-22 coordinate pulmonary immune defense. *Immunol Rev* (2014) 260:129–44. doi: 10.1111/imr.12183