Journal of Pioneering Medical Sciences
Received: January 28, 2026 | Accepted: April 03, 2026 | Published: April 15, 2026
Volume 15, Issue S01, Pages 103-109

DOI https://doi.org/10.47310/jpms202515S0121

Interferon Response in COVID-19: Evidence from Airway Epithelial Cell Models

Muneef M. Aldhafeeri[1*]
[1]Department of Clinical Laboratories Sciences, College of Applied Medical Sciences, University of Hafr Al-Batin, Hafr Al-Batin 39524, Saudi Arabia

*Corresponding author: Muneef M. Aldhafeeri (e-mail: muneef@uhb.edu.sa).

Abstract The Coronavirus Disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has posed significant challenges in understanding host antiviral immune responses. Among these, interferons (IFNs) play a critical role as the first line of defence against viral infections. IFNs are classified into three major types: type I, type II and type III, each contributing to antiviral immunity by activating interferon-stimulated genes that inhibit viral replication. This review aims to summarise current evidence regarding the role of interferons in SARS-CoV-2 infection, with a particular focus on airway epithelial cell models. These models are especially valuable as they closely mimic the structural and functional characteristics of the human respiratory epithelium, including the expression of Angiotensin-Converting Enzyme 2 (ACE2) receptors, thereby providing a physiologically relevant platform for studying viral entry, replication and host immune responses. A comprehensive literature search was conducted on 15 July 2025 using databases and keywords including “airway epithelial cells,” “SARS-CoV-2,” “COVID-19,” and “interferon.” A total of 86 articles were identified, of which 50 were included based on predefined relevance criteria, including studies focusing on interferon responses in airway epithelial models, experimental or clinical relevance to SARS-CoV-2 infection and availability of full-text articles in English. The findings indicate that interferon responses vary depending on cell type, viral variants and host factors such as age and environmental exposure. In conclusion, interferons play a pivotal role in the pathogenesis and potential treatment of COVID-19. Airway epithelial cell models remain essential tools for elucidating these mechanisms and for developing targeted antiviral therapies.

Key Words Immunology, IFN, Covid-19, SARS-CoV-2, Epthileial, Cell Cutlure

INTRODUCTION

Covid-19

Coronaviruses represent a significant category of single-stranded positive-sense RNA viruses. Seven kinds of coronaviruses are recognized as infecting humans. The diverse set includes four seasonal coronaviruses (229E, OC43, NL63 and HKU1) and three highly pathogenic coronaviruses (SARS-CoV, MERS-CoV and SARS-CoV-2). SARS-CoV-2 is the pathogenic virus responsible for the illness named COVID-19 [1]. COVID-19 has made the identification and treatment of respiratory viral infections much more difficult [2]. Although classified as a pulmonary disease, COVID-19 is associated with a range of respiratory and non-respiratory syndromes, including cardiovascular, vascular, renal and neurological [3]. COVID-19 infections can damage airway and lung epithelium: provoking excessive mucus secretion, inflammation and fibrosis [2]. COVID-19 can present with fever, a dry cough, difficulty breathing, loss of smell and loss of taste. Severe COVID-19 can result in death due to low blood oxygen levels, respiratory failure, or a combination of both [4]. The virus gains entry into the body by binding to the Angiotensin-Converting Enzyme 2 (ACE2) receptor, which is overexpressed on the nasal epithelium. ACE2 is known as a counter-injury protective effector in the setting of lung injury [5,6]. The rationale for focusing on airway epithelial cell cultures in this review lies in their superior physiological relevance compared with commonly used experimental models. While animal models provide insights into systemic disease, their applicability is limited by interspecies differences in immune responses and viral receptor expression. Similarly, standard immortalized cell lines, such as Vero E6, lack key components of the interferon signaling pathway, reducing their ability to accurately represent host antiviral mechanisms. In contrast, airway epithelial cell cultures closely mimic the structural and functional characteristics of the human respiratory epithelium, including differentiation into specialized cell types and expression of ACE2 receptors required for SARS-CoV-2 entry.

Importantly, these models retain intact interferon responses, allowing for a more accurate evaluation of viral-host interactions and innate immune dynamics. Therefore, airway epithelial cultures provide a more reliable and biologically relevant platform for studying interferon responses in SARS-CoV-2 infection [5,6].

This review aims to critically analyze interferon responses in SARS-CoV-2 infection using airway epithelial models, focusing on mechanisms, comparative model insights, and therapeutic implications rather than providing a purely descriptive overview. This was a narrative review conducted to evaluate the role of interferon responses in SARS-CoV-2 infection using airway epithelial cell models. A comprehensive literature search was performed on 15 July 2025 using databases such as web of science with keywords including "airway epithelial cells," "SARS-CoV-2," "COVID-19," and "interferon." A total of 86 articles were identified, of which 50 were included based on predefined inclusion criteria, including studies focusing on interferon responses in airway epithelial models, relevance to SARS-CoV-2 infection, and availability of full-text articles in English. Studies not meeting these criteria or lacking sufficient data were excluded. Relevant data were extracted and synthesized to provide an analytical overview of interferon mechanisms, model-based differences, and therapeutic implications (Figure 1).

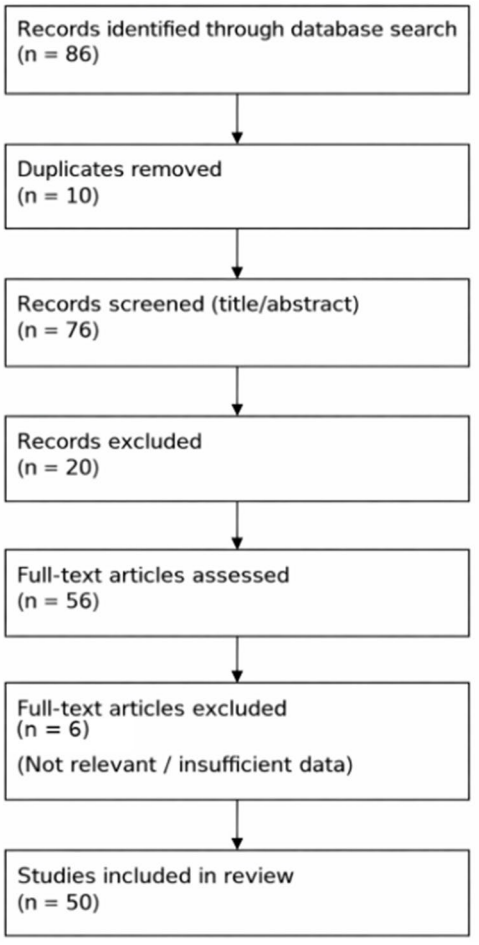

Figure 1: PRISMA flow diagram of study selection process

Interferons

The IFNs system serves as a robust defense against viral infections. IFNs are categorized over three primary categories: I, II and III, according to the receptors they utilize. Type I IFNs consist of IFN-α and IFN-β, type II IFNs consist of IFN-γ and type III IFNs consist of IFN-λ1–4 [7]. IFN-α/β interact with their heterodimeric receptor composite, consisting of interferon alpha/beta receptor 1 and 2 (IFNAR1, IFNAR2), found on nearly all nucleated cells. IFN-λ interact with a distinctive receptor complex that is constituted of the specific interferon lambda receptor 1 (IFNLR1), which is expressed by epithelial cells and specific immune cells [6]. Type I and III IFNs have the ability to limit replication and assembly of viruses [8]. Released IFNs have antiviral effects through autocrine or paracrine. This process activates multiple signaling pathways that encourage the expression of Interferon-Stimulated Genes (ISGs) including CXCL10, ISG15 and MX1, which play a crucial role in limiting viral replication [9]. The initial stage of viral replication, during which the virus is producing copies of itself, can be halted by IFNs [10].

The Role of IFN in COVID-19

Different Cell Types Produce Different IFNs: Human airway epithelial cell cultures are commonly utilized to model pulmonary conditions. These systems facilitate epithelial cell differentiation and replicate the essential characteristics of the mucosal epithelium. Infecting ALI systems with viruses may simulate diverse mechanisms of infectious disease. The therapeutic potential of IFN for treating COVID-19 are underscored by the fact that the virus replicates in these models during COVID-19 and IFNs can inhibit viral infection [11]. Studying the essential characteristics and behaviors of the airways is critical for developing therapeutic strategies for COVID-19 [2]. Therefore, developing human model systems is essential for evaluating viral pathology and testing therapeutics [12].

Shi *et al.* [13] demonstrated that Omicron induced a type-I IFN response in Primary Human Nasal Tissue (PHNT). Entry mediated by metalloproteinases allowed the Omicron spike protein to avoid interferon-inducible factors that target viral entrance. These results may help explain why Omicron is easier to spread and can replace SARS-CoV-2 that exhibits sensitivity to IFN. Furthermore, Castaneda *et al.* [14] investigated of PHNT cells subjected to SARS-CoV-2 and its variations (Beta, Delta and Omicron BA.1 subvariant). They demonstrated that all variations transcriptionally elicited an inflammatory immune response and IFN markers. Another study done by Gamage *et al.* [15] revealed that cells with severe infections have less expression of ISGs compared to uninfected cells in PHNT. Moreover, the production of IFN-λ1 and IFN-β were exclusively observed in a restricted subset of cells with infections. Decreased IFN signaling from infected cells may diminish the initiation of anztiviral condition in adjacent cells, accelerating the development of a chronic infection. Their research on therapeutic development aims to enhance viral clearance in immunocompromised individuals

and indicates a crucial function of immune cells in facilitating viral elimination from infected epithelial tissues. In PHNT and Calu-3 cells, Rebendenne *et al.* [16] categorized host cell responses to SARS-CoV-2. Type I and III IFNs generation was robustly stimulated by both cells. The IFN response was incapable to modulate viral reproduction in Calu-3, despite the fact that IFN treatment effectively inhibited viral replication. The utility of the Calu-3 lung cell for the investigation of viral propagation and innate immunity was validated by the observation of interferon induction in reaction to SARS-CoV-2. Vanderheiden *et al.* [17] employed PHNT cultures to reproduce the SARS-CoV-2. They showed no type I or III IFN response. However, activation of antiviral effector genes was associated to the significant suppression of viral replication in PHNT by pretreatment and posttreatment with these IFNs. This study illustrates the potential therapeutic applications of both type I and III IFNs for COVID-19 patients by utilizing PHNT cultures to replicate SARS-CoV-2 infection. Mulay *et al.* [18] showed that SARS-CoV-2 infection initiates interferon signaling in Human Primary Bronchial Epithelial Cells (HPBECs). SARS-CoV-2-infected cells have been shown to generate an proinflammatory reaction through the upregulation of ISG activity. Additionally, a significant decrease in viral infection was noted following the administration of IFN-β1 to HPBEC. Loo *et al.* [19] demonstrated that alphacoronavirus 229E-CoV (229E) and betacoronavirus OC43-CoV replicated in HPBECs, which was related to specific antiviral response patterns marked by increased production of IFNs type I/III and ISGs in the case of 229E. Robinot *et al.* [20] found that SARS-CoV-2 triggered significant IFN release, primarily facilitated by type III IFN. Furthermore, they found that IFN-λ was secreted in abundance, while IFN-β secretion was restricted and IFN-α was undetectable. They also observed that pretreatment with IFN-β or IFN-λ significantly reduced replication of the virus in HPBECs. Fiege *et al.* [21] demonstrated the rare initiation of IFN production in infected normal Human Tracheal Bronchial Epithelial (nHTBE) cells. Their data indicate that epithelial cells represent the primary cell mainly infected by SARS-CoV-2, highlighting the complexity of antiviral responses and the variability among infected cells. In an additional study, Wang *et al.* [22] examined an airway epithelial substrate constructed from human induced Pluripotent Stem Cells (iPSCs) that was infected with SARS-CoV-2. iPSC cells demonstrate substantial both type I and III IFN and inflammatory productions. For instance, Alpha exhibited marginally reduced sensitivity to IFNs compared to NL-02-2020, whereas other variants demonstrated heightened sensitivity. It is possible that this argument is compelling. The least inhibition by exogenous IFNs was observed in Omicron BA.1 across all cellular models [7]. Banerjee *et al.* [23] demonstrated that SARS-CoV-2 induces a type I IFN productions in vitro in mild COVID-19, utilizing Vero E6 and Calu-3 cells infected with the virus. Furthermore, it was observed that SARS-CoV-2 infection induces the expression of type I IFN and downstream ISGs. This factor is essential in the advance of type I interferons as therapeutic agents. Lokugamage *et al.* [24] indicated that SARS-CoV-2 and SARS-CoV exhibit comparable viral reproduction; however, SARS-CoV-2 is significantly more susceptible to IFN-I. They also showed that IFN-I pretreatment significantly reduces SARS-CoV-2 levels, whereas SARS-CoV remains unaffected. Bordoni *et al.* [25] demonstrated that SARS-CoV-2 infection leads to alterations in endothelial p21, that can be moderately mitigated by reducing IFN-β release from endothelial cells in co-culture with HPBEC.

Drugs Targeting IFN

The human Oxysterol-Binding Protein (OSBP) may facilitate the replication of several positive-sense (+) single-stranded RNA (ssRNA) viruses, , a natural composite and OSBP inhibitor, exhibited antiviral efficacy to multiple infective (+) ssRNA viruses, as indicated by Subramaniyan *et al.* [9]. The administration of OSW-1 in HPBEC affects the synthesis of antiviral innate immune mediators, including IFNB1, IFNL3, CXCL10, ISG15 and MX1. OSW1 enhanced the activation of specific type I and III IFN antiviral responses induced by the RNA virus. JQ-1 and other iBETs may prevent SARS-CoV-2 infection. Mhlekude *et al.* [26] propose that JQ-1 and other iBETs may direct SARS-CoV-2 into interferon development traps for immunological removal. *In vitro* in PHNT cultures and in vivo in mouse models, Finney *et al.* [27] evaluated the impact of Inhaled Corticosteroids (ICSs) administration on pulmonary ACE2 expression. COPD patients and animals exhibiting elastase-induced COPD-like alterations demonstrate reduced ACE2 expression. This was discovered through the injection of ICS. The inhibition of IFN-I by ICS is mechanistically linked to the downregulation of ACE2.

Broadbent *et al.* [3] showed that an endogenously triggered IFN-λ1 mechanism provides immunity to SARS-CoV-2. They additionally noted heightened endogenous release of IFN and subsequent antiviral ISGs. Prophylactic IFN-λ therapy of PHNT sensitive to infections resulted in reduced virus titers. Their data supports the investigation of IFN-λ as a treatment for covid-19. Schuhenn *et al.* [28] showed that the prophylactic application of various IFN-α subtypes in HPBEC through infection of SARS-CoV-2 resulted in unique functional categories of antiviral IFNs, classified as high, middle and low efficacy. For instance, IFN-α5 exhibited enhanced antiviral efficacy to SARS-CoV-2 infection. They also verified the enhanced efficacy of combining IFN-I therapy with remdesivir, along with significant antiviral effects when IFN-α5 was administered independently. Their data display that elevated antiviral IFN-I helps antiviral host effector responses, which may enable the identification of cellular effectors for targeting in innovative therapeutic strategies against SARS-CoV-2 infection. Additionally, Hatton *et al.* [29] presented that the host response is regulated by ISG products and type I and III IFNs. Furthermore, they showed that recombinant IFN-β or IFN-λ1 induced a potent antiviral state that substantially minimized the proliferation of SARS-CoV-2, thereby protecting the integrity of the epithelial barrier. Adult PHNT cells undergo a substantial antiviral response subsequent to exogenous IFN-I/III treatment, suggesting that recombinant IFN-β or IFN-λ1 may have clinical potential in the

chemoprophylaxis and therapitic of COVID-19. Sposito *et al.* [30] found that COVID-19 is more prevalent in the upper respiratory tract, while enhanced IFN-III levels protect and cause mild illness. Conversely, lower respiratory tract in COVID-19 indvidual exhibit increased IFN-λ and IFN-III, cellular apoptosis and a decrease in ISGs. This highlights the significance of the timing of the generation and delivery of interferons during COVID-19. The rapid delivery of particular recombinant IFN-III may serve as a viable treatment option and targeting the upper airways is the most effective method to harness the antiviral properties of interferons. Stimulator of Interferon Genes (STING) is a vital component of the host's defense systems against microbial infections. Significantly, STING activation elicits downstream antiviral immunological responses, encompassing the synthesis of type I and type III IFNs and ISGs [31,32].

IFN Genes

The alveolospheres of SARS-CoV-2 were found to have increased amounts of innate and antiviral immunology, which included IFN and NF-kB, by Dagher *et al.* [33]. Wang *et al.* [34] revealed that the lack of initiation of IFN-related gene expression is a significant distinction between highly pathogenic coronaviruses and less deadly viruses like HCoV-229E or OC43. Supplementation of IFN-λ1 in cell cultures during infection resulted in decreased levels of SARS-CoV-2, indicating a potential function for the inhibition of IFN-mediated antiviral defenses. Wyler *et al.* [35] found that a restricted number of infected cells expressed IFN beta/lambda genes and proinflammatory cytokines, such as IL-6. Their results suggested that the transcriptional activities of IRFs occur prior to those of NF-kB. Yin *et al.* [36] demonstrated that the MDA5 pattern recognition receptor detects viral RNA, which induces a delayed IFN response in response to SARS-CoV-2 replication. They shown that the IFN release caused by SARS-CoV-2 is depending upon the presence of Interferon Regulatory Factor 3 (IRF3), IRF5 and NF-kB/p65.

Assou *et al.* [11] found that the expression of ISGs, was significantly increased by day 4 after SARS-CoV-2 infection. This indicates that the virus has activated the IFN and immune responses. Ravindra *et al.* [37] found that the virus triggers cell-intrinsic expression of type I and type III IFNs, leading to the initiation of ISGs. Lieberman *et al.* [38] shown that no initiation of ISGs obsrved after three days SARS-CoV-2 infections.

IFN, Other Diseases and Complications

The relatively small amount of co-infection incidents identified following the start of the pandemic has resulted in poorly characterized relations between SARS-CoV-2 and other respiratory viruses [39]. Using differentiated human pulmonary bronchial epithelial cell cultures, Cheemarla *et al.* [40] simulated coinfections of Influenza A Virus (IAV) and SARS-CoV-2. In comparison to SARS-CoV-2, the replication of IAV elicited a more robust IFN response and inhibited SARS-CoV-2 reproduction. Their data demonstrate the possible impact of disturbances in one viral infection on the fate of a co-infecting virus. Fage *et al.* [39] found that influenza A(H1N1) pdm09 inhibits following SARS-CoV-2 replication via an IFN-dependent mechanism, whereas respiratory syncytial virus does not show this Essaidi-Laziosi *et al.* [41] conducted a study that examined dual infections, which included the Alpha variant and early-pandemic SARS-CoV-2, as well as three viruses: Rhinovirus (RV) and influenza A and B viruses (IAV and IBV). In co-infections, the limited recovery of SARS-CoV-2 replication was facilitated by neutralizing antibodies that target type I and III IFNs. Blume *et al.* [42] identified a distinct short isoform of ACE2 in the airway epithelium, which serves as the primary site for SARS-CoV-2 infection. Short ACE2 levels increase significantly following IFN stimulation and RV infection, but not in the case of SARS-CoV-2 infection. In instances of interferon inhibition, for example SARS-CoV-2, or IFN-β insufficiency, as observed in asthma, reduced ACE2 synthesis is not commonly observed. Radzikowska *et al.* [43] demonstrated that RV infection in asthmatic patients causes significant activation of the RIG-I inflammasome, thereby diminishing its capacity for type I/III IFN reactions. This leads to primary diminished function, inhibited viral elimination and persistence inflammation. Cheemarla *et al.* [44] showed that prior RV infection augmented ISG responses and inhibited SARS-CoV-2 multiplication. On the other hand, inhibiting ISG induction before SARS-CoV-2 infection raised viral replication.

COPD associated with smoking might be a important hazard for people with COVID-19. Chen *et al.* [45] assessed the impact of Cigarette Smoke (CS) on the immunological and inflammatory responses induced by SARS-CoV-2, in addition to its outcome on the integrity of the epithelial barrier, which resulted in airway epithelial injury. Brocke *et al.* [46] examined the correlation between SARS-CoV-2 infection in PHNT and exposure to Woodsmoke Particles (WSPs). SARS-CoV-2 infection alone elevated type I and III IFNs, ISGs and chemokines in PHNT, triggering a strong transcriptional response. However, the expression of IFN was diminished prior to infection due to previous exposure to WSPs. After temporary exposure to CS, Purkayastha *et al.* [47] infected primary human nonsmoker Airway Basal Stem Cells (ABSCs) with SARS-CoV-2. The IFN response is augmented by SARS-CoV-2 infection, whereas it is impaired by short-term corticosteroid exposure.

The Effect of Temperature on IFN of COVID-19

The replication mechanisms of a variety of respiratory viruses, including RV, influenza viruses, and coronaviruses, are believed to be influenced by the physiological relationship between the upper and lower respiratory tracts, in addition to their varying ambient temperatures [48]. Otter *et al.* [49] showed that common cold-associated human rhinovirus-16 (HRV-16) and human coronaviruses (HCoV-229E, -NL63) respond differently to temperature changes. Antiviral IFN signaling, viral clearance, and better replication at 33°C nasal airway temperature reduces host IFN responses. V'Kovski *et al.* [48] conducted a study investigating the effect of temperature on SARS-CoV-2 and SARS-CoV infections utilizing the HPBEC. SARS-CoV-2 replicated to higher titers during infections conducted at 33°C compared to 37°C, in contrast to SARS-CoV. Both viruses

Table 1: Interferon Responses in SARS-CoV-2 Using Airway Epithelial Models

Study/Author	Model Used	IFN Type Studied	Key Findings	Clinical/Research Implication
Vanderheiden *et al.* [17]	Primary human nasal epithelial cells (PHNT)	Type I, III	IFN pretreatment significantly reduced viral replication	Supports early IFN therapy in COVID-19
Rebendenne *et al.* [16]	PHNT, Calu-3 cells	Type I, III	Strong IFN induction but limited control of viral replication in some cells	Suggests viral evasion of IFN response
Mulay *et al.* [18]	Human Bronchial Epithelial Cells (HPBEC)	Type I (IFN-β)	IFN-β reduced viral infection and induced inflammatory response	Highlights therapeutic potential of IFN-β
Robinot *et al.* [20]	HPBEC	Type III (IFN-λ)	High IFN-λ production with significant antiviral activity	IFN-λ may be key in mucosal immunity
Banerjee *et al.* [23]	Vero E6, Calu-3	Type I	SARS-CoV-2 induces IFN and ISGs in mild infection	Basis for IFN-based therapies
Lokugamage *et al.* [24]	Cell lines	Type I	SARS-CoV-2 more sensitive to IFN than SARS-CoV	Explains differences in viral behavior
Schuhenn *et al.* [28]	HPBEC	Type I (subtypes)	IFN-α5 showed highest antiviral activity	Potential for subtype-specific therapy
Hatton *et al.* [29]	PHNT	Type I, III	Recombinant IFNs reduced viral spread and protected epithelium	Supports prophylactic IFN use
Broeckel *et al.* [32]	Experimental models	Type I, III	STING activation induces IFN but may increase inflammation	Balance needed in therapy
Du *et al.* [2]	Airway stem cells	Type I, III	MSC co-culture reduced viral pathology via IFN modulation	Future regenerative + IFN therapy
Cheemarla *et al.* [40]	Bronchial epithelial cells	Type I, III	Influenza-induced IFN suppressed SARS-CoV-2 replication	Viral interference concept
Otter *et al.* [49]	Airway epithelial models	Type I, III	Lower temperature reduced IFN response → ↑ viral replication	Explains upper airway susceptibility
Mhlekude *et al.* [26]	PBMC + epithelial models	Type I	Stronger IFN response in children	Explains milder pediatric disease

exhibited significant sensitivity to pretreatment with IFN type I and II. Herder *et al.* [50] demonstrated that tissue temperature is a crucial factor in the modulation of SARS-CoV-2 infection. Elevated temperatures (≥39°C) suppressed the replication and spread of SARS-CoV-2, regardless of the activation of IFN-mediated antiviral immune responses.

DISCUSSION

SARS-CoV-2 infections may lead to significant harm to the airway and lung epithelium, including mucus hypersecretion, pulmonary inflammation and fibrosis. Type I and II IFNs have been posited to diminish viral replication and assembly. For example, the severity of COVID-19 may be reduced by the rapid and efficient production of interferons in the lungs. Various respiratory epithelial cells have been utilized, showcasing numerous in vitro systems to investigate the pathophysiology of and formulate therapeutic methods for SARS-CoV-2 patients. This includes the utilization of HPBEC, PHNT and cell lines such as Calu-3. Numerous drugs, including PAV-104, JQ-1, ICS and indomethacin, may delay viral replication, at least in part by inducing IFN, suggesting their potential as treatment options for COVID-19. The therapeutic efficacy of these medications may be further augmented through combination therapy, including oral antiviral agents or certain IFNs. The relations of SARS-CoV-2 with other respiratory viruses may influence the severity of COVID-19 and potentially offer novel strategies for the inhibition of respiratory viral infections. These could also be controlled by modulation of the IFN response. Temperature differences within the lung may also be important to restrict viral replication via IFN, suggesting that early innate immunity is a vital controller of disease severity. Finally, young individual less prone to experience severe symptoms of COVID-19 than adult patients due to differences in the innate immune response. A clearer translational perspective should be incorporated by explicitly addressing how findings from in vitro airway epithelial models relate to clinical outcomes while acknowledging their limitations. Although these models provide valuable insights into early viral entry, replication and interferon-mediated antiviral responses, they do not fully capture the complexity of in vivo conditions, including systemic immune interactions, vascular involvement and patient-specific factors. Therefore, results from epithelial cultures are most applicable to understanding early-stage infection and guiding timing-sensitive interventions, such as early interferon therapy, but may not fully predict outcomes in advanced or severe disease. Integrating this with a discussion of disease stage, the timing of interferon responses and differences between experimental models would strengthen the manuscript by linking mechanistic findings to clinical relevance and therapeutic decision-making.

Limitations

This review has several limitations. First, as a narrative review, it lacks the methodological rigor of a systematic review or meta-analysis, including potential selection bias in study inclusion. Second, the literature search was limited to English-language, full-text articles, which may have excluded relevant studies and introduced language bias. Third, most included studies were based on in vitro airway epithelial models, which, while physiologically relevant, do not fully replicate the complexity of in vivo human immune responses, limiting direct clinical applicability. Additionally, heterogeneity in experimental designs, cell types and interferon assessment methods across studies may affect the comparability of findings.

CONCLUSION

Interferons play a central role in the host defense against SARS-CoV-2, particularly during the early stages of

infection within the airway epithelium. Evidence from airway epithelial cell models highlights the importance of timely and robust interferon responses in limiting viral replication, while delayed or impaired signaling contributes to disease progression.

REFERENCES

[1] Wang, Y. *et al.* "Combating pan-coronavirus infection by indomethacin through simultaneously inhibiting viral replication and inflammatory response." *iScience*, vol. 26, no. 9, 2023, p. 107631. https://doi.org/10.1016/j.isci.2023.107631.

[2] Du, S. *et al.* "Airway basal stem cells inflammatory alterations in COVID-19 and mitigation by mesenchymal stem cells." *Cell Proliferation*, 2025, e13812. https://doi.org/10.1111/cpr.13812.

[3] Broadbent, L. *et al.* "An endogenously activated antiviral state restricts SARS-CoV-2 infection in differentiated primary airway epithelial cells." *PLoS One*, vol. 17, no. 4, 2022, e0266412. https://doi.org/10.1371/journal.pone.0266412.

[4] Chen, Q. *et al.* "ACE2 expression in organotypic human airway epithelial cultures and airway biopsies." *Frontiers in Pharmacology*, vol. 13, 2022, p. 813087. https://doi.org/10.3389/fphar.2022.813087.

[5] Ziegler, C.G.K. *et al.* "SARS-CoV-2 receptor ACE2 is an interferon-stimulated gene in human airway epithelial cells." *Cell*, vol. 181, no. 5, 2020, pp. 1016–1035. https://doi.org/10.1016/j.cell.2020.04.035.

[6] Wang, X. *et al.* "Single-cell transcriptomics reveals a compartmentalized antiviral interferon response in the nasal epithelium of mice." *Journal of Virology*, vol. 99, no. 3, 2025, e01413-24. https://doi.org/10.1128/jvi.01413-24.

[7] Nchioua, R. *et al.* "Reduced replication but increased interferon resistance of SARS-CoV-2 Omicron BA.1." *Life Science Alliance*, vol. 6, no. 6, 2023, e202201862. https://doi.org/10.26508/lsa.202201862.

[8] Zaleska, A. *et al.* "IFN lambda deficiency contributes to severe COVID-19 outcomes." *International Journal of Molecular Sciences*, vol. 25, no. 19, 2024, p. 10719. https://doi.org/10.3390/ijms251910719.

[9] Subramaniyan, B. *et al.* "Anti-SARS-CoV-2 small molecule targeting of oxysterol-binding protein activates antiviral innate immunity." *ACS Infectious Diseases*, vol. 11, no. 5, 2025, pp. 1064–1077. https://doi.org/10.1021/acsinfecdis.4c00680.

[10] Vanderwall, E.R. *et al.* "Airway epithelial interferon response to SARS-CoV-2 Is inferior to rhinovirus and heterologous rhinovirus infection suppresses SARS-CoV-2 replication." *Scientific Reports*, vol. 12, no. 1, 2022, p. 6972. https://doi.org/10.1038/s41598-022-10921-1.

[11] Assou, S. *et al.* "Transcriptome landscape of the *in vitro* human airway epithelium response to SARS-CoV-2." *International Journal of Molecular Sciences*, vol. 24, no. 15, 2023, p. 12177. https://doi.org/10.3390/ijms241512177.

[12] Rajan, A. *et al.* "The human nose organoid respiratory virus model." *mBio*, vol. 13, no. 1, 2022, e03511-21. https://doi.org/10.1128/mbio.03511-21.

[13] Shi, G. *et al.* "Omicron spike confers enhanced infectivity and interferon resistance." *Nature Communications*, vol. 15, no. 1, 2024, p. 889. https://doi.org/10.1038/s41467-024-45171-2.

[14] Castaneda, D.C. *et al.* "Spatiotemporally organized immunomodulatory response to SARS-CoV-2." *iScience*, vol. 26, no. 8, 2023, pp. 107374. https://doi.org/10.1016/j.isci.2023.107374.

[15] Gamage, A.M. *et al.* "Human nasal epithelial cells sustain persistent SARS-CoV-2 infection." *mBio*, vol. 13, no. 1, 2022, e03436-21. https://doi.org/10.1128/mbio.03436-21.

[16] Rebendenne, A. *et al.* "SARS-CoV-2 triggers an MDA-5-dependent interferon response." *Journal of Virology*, vol. 95, no. 8, 2021, e02415-20. https://doi.org/10.1128/JVI.02415-20.

[17] Vanderheiden, A. *et al.* "Type I and III interferons restrict SARS-CoV-2 Infection." *Journal of Virology*, vol. 94, no. 19, 2020, e00985-20. https://doi.org/10.1128/JVI.00985-20.

[18] Mulay, A. *et al.* "SARS-CoV-2 infection of primary human lung epithelium." *Cell Reports*, vol. 35, no. 5, 2021, pp. 109055. https://doi.org/10.1016/j.celrep.2021.109055.

[19] Loo, S.L. *et al.* "Human coronaviruses 229E and OC43 replicate and induce distinct antiviral responses." *American Journal of Physiology-Lung Cellular and Molecular Physiology*, vol. 319, no. 6, 2020, pp. L926–L931. https://doi.org/10.1152/ajplung.00272.2020.

[20] Robinot, R. *et al.* "SARS-CoV-2 infection induces dedifferentiation of multiciliated cells." *Nature Communications*, vol. 12, no. 1, 2021, pp. 4354. https://doi.org/10.1038/s41467-021-24521-x.

[21] Fiege, J.K. *et al.* "Single-cell resolution of SARS-CoV-2 tropism, antiviral responses and susceptibility to therapies in primary human airway epithelium." *PLoS Pathogens*, vol. 17, no. 1, 2021, e1009292. https://doi.org/10.1371/journal.ppat.1009292.

[22] Wang, R. *et al.* "Human airway lineages derived from pluripotent stem cells reveal epithelial responses to SARS-CoV-2 Infection." *American Journal of Physiology-Lung Cellular and Molecular Physiology*, vol. 322, no. 3, 2022, pp. L462–L478. https://doi.org/10.1152/ajplung.00302.2021.

[23] Banerjee, A. *et al.* "Experimental and natural evidence of SARS-CoV-2 infection–induced activation of type I interferon responses." *iScience*, vol. 24, no. 5, 2021, pp. 102477. https://doi.org/10.1016/j.isci.2021.102477.

[24] Lokugamage, K.G. *et al.* "Type I interferon susceptibility distinguishes SARS-CoV-2 from SARS-CoV." *Journal of Virology*, vol. 94, no. 23, 2020, e01410-20. https://doi.org/10.1128/JVI.01410-20.

[25] Bordoni, V. *et al.* "SARS-CoV-2 infection of airway epithelium triggers endothelial activation and senescence." *Cells*, vol. 11, no. 18, 2022, pp. 2877. https://doi.org/10.3390/cells11182877.

[26] Mhlekude, B. *et al.* "Pharmacological inhibition of BET proteins induces an NRF2-mediated antiviral state." *PLoS Pathogens*, vol. 19, no. 9, 2023, e1011657. https://doi.org/10.1371/journal.ppat.1011657.

[27] Finney LJ *et al.* "Inhaled corticosteroids downregulate ACE2 in COPD via interferon suppression." *Journal of Allergy and Clinical Immunology*, vol. 147, no. 2, 2021, pp. 510–519. https://doi.org/10.1016/j.jaci.2020.09.034.

[28] Schuhenn, J. *et al.* "Differential interferon-α Subtype Signatures Suppress SARS-CoV-2 Infection." *Proceedings of the National Academy of Sciences*, vol. 119, no. 8, 2022, e2119235119. https://doi.org/10.1073/pnas.2119235119.

[29] Hatton, C.F. *et al.* "Delayed induction of type I and III interferons mediates nasal epithelial permissiveness to SARS-CoV-2." *Nature Communications*, vol. 12, no. 1, 2021, pp. 7092. https://doi.org/10.1038/s41467-021-27318-0.

[30] Sposito, B. *et al.* "Interferon landscape along the respiratory tract impacts COVID-19 severity." *Cell*, vol. 184, no. 19, 2021, pp. 4953–4968. https://doi.org/10.1016/j.cell.2021.08.016.

[31] Zhu, Q. *et al.* "Inhibition of coronavirus infection by a synthetic STING agonist." *Antiviral Research*, vol. 187, 2021, p. 105015. https://doi.org/10.1016/j.antiviral.2021.105015.

[32] Broeckel, R. *et al.* "STING agonist–induced innate immune responses against respiratory viruses." *ACS Infectious Diseases*, vol. 10, no. 9, 2024, pp. 3392–3407. https://doi.org/10.1021/acsinfecdis.4c00258.

[33] Dagher, R. *et al.* "Human iPSC-based COPD model to investigate SARS-CoV-2 outcomes." *Stem Cells*, vol. 42, no. 3, 2024, pp. 230–250. https://doi.org/10.1093/stmcls/sxad090.

[34] Wang Y *et al.* "SARS-CoV-2-Infected Airway Epithelial Cultures Lack Interferon Responses." *Clinical and Translational Immunology*, vol. 13, no. 4, 2024, e1503. https://doi.org/10.1002/cti2.1503.

[35] Wyler, E. *et al.* "Transcriptomic profiling identifies HSP90 as a COVID-19 therapy target." *iScience*, vol. 24, no. 3, 2021, p. 102151. https://doi.org/10.1016/j.isci.2021.102151.

[36] Yin, X. *et al.* "MDA5 governs innate immune response to SARS-CoV-2." *Cell Reports*, vol. 34, no. 2, 2021, p. 108628. https://doi.org/10.1016/j.celrep.2020.108628.

[37] Ravindra NG *et al.* "Single-cell longitudinal analysis of SARS-CoV-2 infection in airway epithelium." *PLoS Biology*, vol. 19, no. 3, 2021, e3001143. https://doi.org/10.1371/journal.pbio.3001143.

[38] Lieberman, N.A.P. *et al.* "*In vivo* antiviral host transcriptional response to SARS-CoV-2." *PLoS Biology*, vol. 18, no. 9, 2020, e3000849. https://doi.org/10.1371/journal.pbio.3000849.

[39] Fage, C. *et al.* "Influenza A(H1N1)pdm09 but Not RSV interferes with SARS-CoV-2 replication." *Viruses*, vol. 14, no. 2, 2022, pp. 277. https://doi.org/10.3390/v14020277.

[40] Cheemarla, N.R. *et al.* "Viral interference during influenza A–SARS-CoV-2 coinfection." *Journal of Infectious Diseases*, vol. 229, no. 5, 2024, pp. 1430–1434. https://doi.org/10.1093/infdis/jiad593.

[41] Essaidi-Laziosi, M. *et al.* "Sequential infections modulate SARS-CoV-2 replication." *Emerging Microbes & Infections*, vol. 11, no. 1, 2022, pp. 412–423. https://doi.org/10.1080/22221751.2022.2032375.

[42] Blume C *et al.* "Novel ACE2 Isoform in Respiratory Epithelia." *Nature Genetics*, vol. 53, no. 2, 2021, pp. 205–214. https://doi.org/10.1038/s41588-020-00759-x.

[43] Radzikowska U *et al.* "Rhinovirus-Induced Epithelial Inflammasome Suppresses Antiviral Immunity." *Nature Communications*, vol. 14, no. 1, 2023, pp. 2329. https://doi.org/10.1038/s41467-023-38035-6.

[44] Cheemarla, N.R. *et al.* "Dynamic innate immune response determines SARS-CoV-2 susceptibility." *Journal of Experimental Medicine*, vol. 218, no. 8, 2021, e20210583. https://doi.org/10.1084/jem.20210583.

[45] Chen, R. *et al.* "SARS-CoV-2 infection aggravates cigarette smoke–exposed airway damage." *Virology Journal*, vol. 20, no. 1, 2023, p. 65. https://doi.org/10.1186/s12985-023-01992-1.

[46] Brocke, S.A. *et al.* "Woodsmoke exposure alters antiviral response to SARS-CoV-2." *American Journal of Physiology-Lung Cellular and Molecular Physiology*, vol. 322, no. 3, 2022, pp. L479–L494. https://doi.org/10.1152/ajplung. 00412.2021.

[47] Purkayastha, A. *et al.* "SARS-CoV-2 and cigarette smoke increase infection severity." *Cell Stem Cell*, vol. 27, no. 6, 2020, pp. 869–875. https://doi.org/10.1016/j.stem.2020.11.007.

[48] V'Kovski, P. *et al.* "Temperature-dependent virus-host dynamics for SARS-CoV-2." *PLoS Biology*, vol. 19, no. 3, 2021, e3001158. https://doi.org/10.1371/journal.pbio.3001158.

[49] Otter, C.J. *et al.* "Interferon signaling in nasal epithelium distinguishes respiratory viruses." *bioRxiv*, preprint, 2023. https://doi.org/10.1101/2023.01.01.522345.

[50] Herder, V. *et al.* "Elevated temperature inhibits SARS-CoV-2 Replication." *PLoS Biology*, vol. 19, no. 12, 2021, e3001065. https://doi.org/10.1371/journal.pbio.3001065.