

From Acute Respiratory Viral Infection to Post-Viral Inflammation and Tissue Remodelling: Molecular Mechanisms and Therapeutic Perspectives

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Abstract

Viral respiratory infections are among the most prevalent infectious diseases and have clinical effects that extend beyond the acute phase of viral replication. Inflammation is important for antiviral defence and tissue repair, but when excessive, prolonged, or incompletely resolved, it can contribute to persistent respiratory abnormalities. A growing number of studies suggest that post-viral respiratory disease is a multifactorial process involving several interacting pathways, including dysregulated innate immune signalling, epithelial injury, altered immune cell signalling, metabolic and mitochondrial dysfunction, oxidative stress, abnormal cell death, and impaired tissue repair.

This narrative review reviews the literature published in recent years (2020-2026) on the five major respiratory viruses linked to persistent inflammatory responses: SARS-CoV-2, influenza viruses, respiratory syncytial virus (RSV), rhinovirus, and adenovirus. Special emphasis on the role of viral recognition by

pattern recognition receptors, interferon signalling, NF- κ B and mitogen-activated protein kinase pathways, activation of inflammasomes, cellular interactions, mitochondrial dysfunction, immunometabolic changes, and tissue remodelling. We will evaluate evidence of a prolonged presence of viral material or altered host responses separately from evidence of continued productive viral replication.

No single mechanism in the available literature explains persistent respiratory disease. SARS-CoV-2 has shown ample evidence of post-acute inflammatory and immune abnormalities, whereas influenza, RSV, rhinovirus, and adenovirus exhibit unique patterns of epithelial injury, immune activation, recurrent inflammation, or persistence. More recent research suggests that respiratory viral infections may also affect epithelial progenitor cell behaviour and their role in subsequent tissue repair. The difference between active viral infection and post-viral inflammatory disease is important from a therapeutic point of view. When viral replication continues, direct antiviral therapy is relevant; when inflammation, tissue remodelling, or fibrosis continues, different approaches may be relevant. Future studies should include longitudinal clinical studies, along with single-cell,

transcriptomic, proteomic, metabolic, and immunological assessments, to identify patients at risk for chronic respiratory disease and develop therapeutic interventions that target the disease's biological stage.

The main topics covered are respiratory viral infections, persistent inflammation, SARS-CoV-2, influenza, respiratory syncytial virus, rhinovirus, adenovirus, innate immunity, epithelial injury, airway remodelling, and fibrosis.

1. Introduction

Worldwide, respiratory viral infection is a significant cause of acute respiratory illness. Influenza viruses, respiratory syncytial virus, rhinoviruses, adenoviruses and coronaviruses are important respiratory pathogens. They cause a wide spectrum of clinical signs, including upper respiratory infection, bronchiolitis, pneumonia, acute respiratory distress syndrome, and worsening of chronic airway disease [1].

Influenza is a key example of the ongoing clinical relevance of respiratory viruses. Influenza A and B viruses remain significant causes of seasonal respiratory disease, and disease severity depends on the virus, host age, underlying disease, and the quality of the immune response [2]. Likewise, RSV is a major cause of LRTI in infants and older adults, and rhinoviruses are a significant cause of wheezing and exacerbations of asthma [3,4]. Adenoviruses can also cause severe respiratory disease, especially in outbreaks and in susceptible groups [5].

The clinical course of infection depends not only on viral replication. Respiratory viral disease is a product of the host response and direct effects of the virus; tissue damage may occur due to direct effects of the virus or immune-mediated processes [1]. This is important because activation of the immune system is necessary for the control of infection. However, excessive or prolonged activation can damage epithelia, cause vascular abnormalities, and remodel tissues.

The respiratory epithelium plays a special role in this process. Epithelial cells are not only a physical barrier but also active participants in innate immunity. Once they recognise the virus, they can secrete interferons, cytokines, chemokines, antimicrobial factors, and other mediators that help communicate with nearby epithelial and immune cells [1,6]. These interactions affect the recruitment and activation of macrophages, neutrophils, dendritic cells, lymphocytes, endothelial cells and fibroblasts.

Inflammation is usually succeeded by a resolution and tissue repair phase. Respiratory epithelial progenitor cells can proliferate and differentiate into epithelial cells to replace injured ones. However, recent data show that an infection with respiratory viruses can cause more persistent changes in the epithelial progenitor cells and their daughter cells. These changes can continue after clinical recovery and may contribute to post-viral lung disease [7].

SARS-CoV-2 has brought this problem to the fore. Some individuals experience symptoms and biological abnormalities that persist following the acute infection, known as post-acute sequelae of SARS-CoV-2 infection (PASC) or 'Long COVID'. Several mechanisms have been suggested, including persistent viral components, immune dysregulation, endothelial abnormalities, metabolic changes, autoimmunity, and persistent inflammatory signalling [8-10]. Importantly, the presence of viral RNA/antigen following acute infection does not necessarily indicate continued productive viral replication. However, viral persistence may contribute to post-acute disease, but it does not fully explain it [9,10].

These principles also apply to other respiratory viruses, though evidence and mechanisms vary. Influenza may cause extensive epithelial injury and affect subsequent repair processes. To some extent, both RSV and rhinovirus can cause long-term changes in lung epithelial cells, and rhinovirus is strongly linked to recurrent airway inflammation and remodelling, particularly in asthma [4,7,11]. Adenovirus is a significant cause of inflammatory lung damage and can persist under certain clinical conditions [5,12].

This narrative review discusses the potential for the development of an acute antiviral response to become chronic inflammatory, or tissue abnormalities caused by a respiratory viral infection. The review emphasises the pathogens SARS-CoV-2, influenza, RSV, rhinovirus and adenovirus. It explores the links between viral sensing, innate immune signalling, cell-to-cell communication, changes in mitochondria and metabolism, cell death, tissue repair/repair remodelling, and therapeutic strategies. This article uses a literature search and review approach.

2. Literature search and review approach

This article is designed to be a narrative literature review. The aim was to gather new evidence on the biological basis of the relationship between respiratory viral infections, chronic inflammation, and long-term respiratory dysfunction. The literature search was conducted mainly from January 2020 through September 2026. We searched PubMed/MEDLINE, Web of Science Core Collection, Scopus, and Google Scholar.

Search terms were merged based on the topic explored and included: respiratory viral infection, persistent inflammation, post-viral inflammation, SARS-CoV-2, influenza, respiratory syncytial virus, rhinovirus, adenovirus, pattern recognition receptors, interferon, NF- κ B, MAPK, inflammasome, mitochondrial dysfunction, oxidative stress, immunometabolism, epithelial repair, airway remodelling, fibrosis, and antiviral therapy.

We preferred peer-reviewed studies, major biomedical reviews, and recent mechanistic studies directly related to the viruses or biological pathways covered in the review. We emphasised human studies for clinical persistence and post-viral disease and used experimental and animal studies to explain mechanisms where human evidence is limited.

We did not produce formal pooled effect estimates or a PRISMA study-selection flow because this is a narrative review, not a systematic review or meta-analysis. Instead, we presented evidence thematically, based on viral mechanisms, host inflammatory responses, cellular interactions, tissue consequences, and therapeutic implications.

3. Acute Infection—Persistent Inflammation

A single pathway from acute respiratory infection to prolonged inflammation is unlikely. Multiple mechanisms may be involved, and their relative contribution can vary by virus, host individual, infection severity, and the respiratory tract state before infection.

During acute infection, viral nucleic acids are recognised by pattern-recognition receptors (PRRs). These receptors trigger signalling pathways that activate interferon regulatory factors and inflammatory transcription factors. Type I and type III interferons support antiviral defence, and cytokines/chemokines activate immune cells in infected tissues [6,13].

When properly managed, this response is protective. However, overactive or sustained innate and adaptive immune activation can mediate tissue damage. Influenza is a good example: Immune responses are a prerequisite for viral clearance, but over-activation of innate or adaptive responses can lead to immunopathology and/or injury of respiratory tissues [14].

A significant advance in this area is the understanding that the effects of a respiratory infection can persist beyond viral replication. Recent studies show that respiratory viruses and the inflammatory environment they trigger can affect gene expression and activity in remaining epithelial progenitor cells. These alterations may persist after the infection clears and could affect future lung repair [7].

This concept alters the understanding of post-viral disease. If symptoms persist, it does not necessarily mean that the virus is still replicating. Rather, the original infection can create a changed cellular and tissue environment that prevents inflammation from resolving completely, repair from occurring, or epithelial restitution.

This distinction is very well demonstrated by SARS-CoV-2. Viral RNA or antigen has been found to persist in some post-acute disease individuals; however, detecting viral components does not prove that a virus is replicating [9,10]. Therefore, chronic immune activation can develop due to viral remnants, immune dysfunction, tissue damage, or a combination of these.

4. Virus-Specific Mechanisms

4.1.SARS-CoV-2

SARS-CoV-2 targets multiple innate immune components. Experimental research shows that the cytosolic RNA sensor MDA5 induces type I and type III interferon after SARS-CoV-2 infection via MAVS and IRF3 [13]. Concurrently, SARS-CoV-2 can disrupt interferon-mediated cell responses, indicating the multifaceted relationship between antiviral immunity and viral immune evasion [13].

Dysregulated inflammatory response has also been linked to severe SARS-CoV-2 infection. Inflammatory mediators such as IL-1 β , IL-18 and others can be produced via activation of inflammasome pathways, including NLRP3-related mechanisms [15]. Long-term effects of SARS-CoV-2 infection are also more complicated. Some tissues retain persistent viral RNA or antigen, and some studies suggest that these persistent viral components may contribute to ongoing immune stimulation [9,10]. Other mechanisms include endothelial dysfunction, immune-cell abnormalities, metabolic alterations, and autoimmunity [8,10].

The evidence therefore favours a multifactorial model, rather than the “persistent virus equals persistent disease” model. Interestingly, the epithelial responses are not always the same from respiratory viruses. Both SARS-CoV-2 and H1N1 influenza stimulated interferon-associated transcriptional responses in bronchial epithelial cells, and under the experimental conditions tested, H1N1 disrupted the epithelium more and elicited a more robust inflammatory protein response [16]. These results highlight the significance of virus-specific mechanisms.

4.2. Influenza

Influenza A and B viruses enter respiratory epithelial cells and trigger multiple innate immune pathways. Toll-like receptors and RIG-I-like receptors can also detect viral RNA, activating TBK1, NF- κ B, IRF3/7, MAVS, and related pathways [14].

The interferon response helps to limit viral replication and stimulate adaptive immunity. Inflammatory signalling can also cause tissue injury, however. Neutrophil recruitment, macrophage activation, cytokine production, and epithelial cell death can become harmful if the response is too strong [14].

The repair phase can also be affected. Recent studies have focused on the impact of influenza infection on the fates of lung epithelial cells, and on responses of lung progenitor cells. The behaviour of any epithelial progenitors that remain after viral injury may be altered by the inflammatory environment, which in turn can affect long-term tissue recovery [7].

This does not mean that all flu infections result in chronic inflammation. Most infections resolve without persistent pulmonary disease. Rather, influenza shows that the severity and quality of the initial inflammatory response can affect subsequent tissue repair.

4.3. Respiratory Syncytial Virus

RSV is an important cause of lower respiratory tract disease in infants and older adults. It is a disease mediated by interactions of infected airway epithelial cells with a variety of immune-cell populations.

RSV can induce innate immune signalling and use viral strategies to modulate and suppress antiviral responses. The balance between antiviral interferon signalling and inflammatory pathways affects the course of infection.

There is recent experimental evidence that links acute RSV infection with subsequent epithelial abnormalities. The authors in Morris et al. Showed changes in the populations of lung epithelial cells that persisted for at least 4 weeks after early-life RSV infection in mice, such as alterations in alveolar epithelial-cell composition and persistent expression of asthma-associated genes. Their results also suggested that the activation of the IL-1 β pathway was involved in these long-term changes [17]

These findings are significant for the concept of tissue memory after a virus. The study used an experimental model, and the magnitude of this mechanism's influence in humans remains unknown.

RSV drug development has also progressed significantly, with several candidate agents targeting the virus's fusion and/or replication processes and monoclonal antibodies being evaluated [3]. These advances highlight the need to differentiate between antiviral therapy during acute infection and interventions for subsequent inflammatory or structural effects.

4.4. Rhinovirus

Rhinovirus is a common respiratory virus and is especially linked to asthma exacerbations. Rhinovirus inhalation is the initial step in invading respiratory epithelial cells and triggering innate immune responses. The epithelial response involves releasing interferon and inflammatory mediators and secreting cytokines, including IL-25, IL-33, and TSLP, which can modulate type 2 immune responses [4,18].

Results vary widely among individuals. While the majority of people suffer a self-limited upper respiratory infection, susceptible people, especially those with asthma, may end up with severe inflammation and bronchoconstriction in the lower respiratory tract [4].

Repeated rhinovirus infections may induce airway remodelling through interactions among vascular cells, airway smooth muscle cells, myofibroblasts, and fibroblasts. There is recent evidence that extracellular matrix deposition, type 2 inflammation and structural changes, which may impair responsiveness to bronchodilator therapy, are involved in rhinovirus-associated remodelling [11].

Therefore, it is more appropriate to consider the role of rhinovirus in chronic respiratory disease in the context of repeated infection, abnormal inflammatory responses, and repeated injury-repair cycles, rather than persistent viral replication.

4.5. Adenovirus

Adenoviruses are DNA viruses that can cause respiratory disease, from a mild upper respiratory tract infection to severe pneumonia. Innate immune recognition and cytokine production play important roles in adenovirus-induced inflammation. In some immunocompromised hosts, disseminated infection can trigger a significant cytokine and chemokine response [12]. There is a growing recognition of immune-mediated tissue injury in adenovirus lung disease in recent years. In relation to the adenoviruses, certain serotypes are associated with outbreaks of respiratory illness and severe disease, including adenovirus types 3, 4, 7 and 14 [5]. Respiratory virus: Adenoviruses are a good example of this type of virus, where inflammation can play a significant role in causing damage. However, be cautious about evidence for long-term respiratory persistence. Persistent adenoviral infection is more likely to be significant in certain groups, such as immunocompromised individuals. However, do not assume it causes chronic inflammation in every person infected with adenoviruses.

5. Pattern-Recognition Receptors and Innate Immune Signalling.

PRRs are the first molecular encounter between respiratory viruses and the host immune system. They recognise pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) and trigger signalling pathways that orchestrate antiviral responses and inflammation [6].

The Toll-like receptors, RIG-I-like receptors and NOD-like receptors are key PRR families. TLR3 is activated by double-stranded RNA, while TLR7 and TLR8 are activated by single-stranded RNA in appropriate intracellular locations. RIG-I and MDA5 detect cytosolic viral RNA and signal through MAVS [6,13]. These pathways are crucial because they are involved in SARS CoV-2 infection. In a popular model of respiratory epithelial cells, induction of type I and III interferon has been reported to depend on MDA5, MAVS and IRF3 [13]. IRF3/7 trigger interferon production, and NF- κ B and MAPK pathways activate inflammatory cytokines and chemokines after PRR activation.

These pathways are not inherently harmful. Their protective effect is crucial in controlling viruses. The challenge arises when activation is off-target, over- or under-resolved, or poorly timed. This chronic inflammatory state can be self-reinforcing, with infected epithelial cells secreting cytokines and chemokines that recruit inflammatory cells, which in turn secrete other inflammatory mediators and ROS. This creates a tissue landscape that keeps inflammation active even when the initial viral stimulus is greatly reduced.

6. Interferon Signalling

The respiratory tract is important in antiviral defence, and interferons are important molecules. Interferon-stimulated genes are activated by type I and type III interferons (IFN α , IFN β and IFN λ) and have antiviral effects on viral replication and spread [13,19]. However, interferon responses

should be considered over time. Prolonged immune activation can cause tissue damage, and early interferon may not be enough to prevent viral replication. Viral infection can also change cells' sensitivity to interferon signalling [13], and MDA5 recognition results in the production of type I and III interferon.

Such pathways do not contain toxic substances per se. They have a protective function which plays a key role in virus control. The challenge is when activation is not targeted, is over-resolved, and/or is poorly timed. This chronic inflammatory state may be self-sustaining such that infected epithelial cells release cytokines and chemokines that attract inflammatory cells, which then release other cytokines, chemokines, and ROS. This establishes a tissue milieu that prevents resolution of inflammation despite the significant reduction in the initial inflammatory stimulus.

7. Inflammasomes in Inflammatory Cell Death

Intracellular signalling platforms like inflammasomes sense danger signals and cell stress. There is a great deal of study of the NLRP3 inflammasome in respiratory viral diseases, particularly. IL-1 β and IL-18 may be matured and secreted as a result of inflammasome activation, and may lead to pyroptosis, a form of programmed inflammatory cell death [15,20].

In the case of pyroptosis, the plasma membrane ruptures, leading to the release of inflammatory mediators. It could play a role in resistance to infection by killing infected cells and can also lead to further tissue damage if pyroptosis is excessive [20]. SARS-CoV-2 infection has been linked to inflammasome activation, and NLRP3-mediated signalling has been suggested as one pathway involved in the inflammatory pathology [15].

The same general rule also applies to other respiratory viruses (though not consistently across all viruses).

Importantly, inflammatory cell death should not be thought of as purely pathological. Antiviral defence involves cell death. The key question is whether the amount of cell death and when it occurs allow adequate clearance and repair, or cause continued tissue injury and inflammation.

8. Mitochondrial Dysfunction and Oxidative Stress

Mitochondria are at the crossroads of metabolism, cellular stress and innate immunity. Viral infection may change mitochondrial metabolism, membrane dynamics, ROS production and mitophagy. Mitochondrial dysfunction may increase ROS production, and mitochondrial danger signals may activate inflammatory pathways [21]. Additionally, the antiviral signalling pathway is directly involved with mitochondria through MAVS, thus creating a crucial link between mitochondrial integrity and viral recognition. Declining mitochondrial function may further exacerbate oxidative stress and inflammation-mediated signalling.

Viral infection triggers mitochondrial stress and ROS/DAMPs, which trigger inflammatory signalling and further cellular stress.

In recent years, there has been greater focus on the key role of mitochondrial dysfunction in oxidative stress and inflammation, which also impairs immune-cell function and inflammasome activation [21].

Many of these, however, are mechanistic and are not specific to respiratory viruses. So, mitochondrial dysfunction may contribute to ongoing disease, but it is not the sole cause of viral respiratory inflammation.

9. Immunometabolism and Metabolic Reprogramming

Host-cell metabolic activity is an important factor in viral replication. Viruses lack independent metabolic systems that allow them to replicate and instead use host metabolic pathways to gain energy and biosynthetic substrates.

SARS-CoV-2 (COVID-19), influenza, and RSV (RSV) respiratory viruses influence glucose metabolism, lipid metabolism, cholesterol homeostasis, mitochondrial function, and oxidative stress [22].

A common metabolic change is increased glycolysis. Increased glycolytic activity may supply ATP quickly and provide biosynthetic intermediates required during infection. Meanwhile, changes in immune-cell metabolism regulate activation and inflammatory phenotype.

This establishes an important link between metabolism and inflammation. Metabolic reprogramming is not only a result of infection, but may also affect viral replication and immune cells [22].

However, the impact of these effects is context-sensitive. Inflammatory injury can occur from stress on metabolic pathways used for antiviral immune responses.

10. Cellular Communication and Tissue Remodelling.

Persistent inflammation involves interactions between cell types, rather than changes in the cells themselves.

Epithelial cells

Epithelial cells detect viral components and then secrete interferons, cytokines, and chemokines. They also modulate immune cell recruitment and are involved in tissue repair [1,7].

Macrophages

Macrophages can help eliminate microbes, initiate inflammatory responses, and repair tissues. Cytokines, metabolic conditions, and signals from damaged epithelial cells influence them.

Neutrophils

Neutrophils are the first line of defence against microbes but can also cause tissue damage via proteases, ROS, and extracellular traps when over-recruited and over-activated.

Endothelial cells

Endothelial dysfunction can affect immune-cell trafficking and increase vascular permeability. This mechanism has been studied in particular detail in severe SARS-CoV-2 infection.

Fibroblasts

Fibroblasts play a greater role in tissue repair. Continuous inflammatory signals can induce them to assume myofibroblast-like features and overproduce extracellular matrix.

Transforming growth factor beta (TGF- β) is a key regulator of fibroblast activation and tissue fibrosis. Dysregulated tissue repair may lead to further ECM deposition, which could drive remodelling of the pulmonary structure and impaired function [23]. A prominent example in this regard is infection with rhinoviruses, which can be repeated and can trigger exacerbations, potentially exacerbating epithelial damage and airway remodelling [11].

11. Post-viral tissue injury, repair and fibrosis

Inflammation is just one component of recovery. Restoring respiratory epithelial structure and function is also necessary.

New research shows that respiratory viral infection can change epithelial progenitor cells and their progeny for long periods. These changes in epithelial regeneration may affect the development of post-viral lung disease [7].

Experimental studies of RSV support this concept. A long-term effect of early-life RSV infection was observed: mice developed lasting changes in epithelial cell composition and in the expression of asthma-associated genes. The changes in these parameters seemed to be mediated by IL-1 β signalling [17].

Influenza may also similarly affect epithelial cell fate and repair after damage [7].

With more severe tissue damage, chronic inflammation can stimulate fibroblasts to deposit extracellular matrix. Pulmonary fibrosis involves epithelial injury, interaction between macrophages, fibroblasts, and TGF- β signalling, and remodelling of the extracellular matrix and abnormal repair [23].

Of importance: fibrosis should not be described as an inevitable consequence of respiratory viral infection. It is better understood as a potential consequence in a limited number of patients following severe or dysregulated tissue damage.

12. Comparative Evidence

Table 1. Principal mechanisms associated with prolonged inflammatory or structural effects of selected respiratory viruses

Virus	Major host-response pathways	Important cellular effects	Potential prolonged consequence	Evidence level
SARS-CoV-2	MDA5-MAVS-IRF3, interferons, NF- κ B, inflammasome pathways	Epithelial and endothelial dysfunction; immune dysregulation	PASC, persistent inflammation, altered tissue repair	Human + experimental
Influenza	RIG-I/TLR pathways, IFN, NF- κ B, inflammatory cytokines	Epithelial injury, immune-mediated tissue damage	Altered epithelial repair and post-viral lung effects	Human + experimental
RSV	IFN pathways, inflammatory cytokines, IL-1 β -related signalling	Airway epithelial injury and altered epithelial-cell states	Airway hyperreactivity, altered repair, asthma susceptibility	Clinical + experimental

Virus	Major host-response pathways	Important cellular effects	Potential prolonged consequence	Evidence level
Rhinovirus	IFN, epithelial cytokines, type 2 inflammatory pathways	Epithelial activation, smooth muscle/fibroblast responses	Recurrent airway inflammation and remodelling	Clinical + experimental
Adenovirus	Innate sensing, cytokine/chemokine pathways	Strong inflammatory responses and lung injury	Severe pulmonary disease; persistence in selected hosts	Clinical + experimental

The evidence does not support a single universal mechanism. Instead, different viruses appear to reach prolonged respiratory dysfunction through overlapping but distinct pathways.

13. Therapeutic Perspectives

The therapeutic implications of persistent respiratory inflammation depend heavily on the stage of disease.

A fundamental distinction should be made between:

1. Active viral replication;
2. Acute immune-mediated tissue injury;
3. Post-viral persistent inflammation; and
4. Established tissue remodelling or fibrosis.

These states should not automatically receive the same therapeutic strategy.

13.1. Direct antiviral therapy

Direct antivirals remain important during active viral replication.

For influenza, neuraminidase inhibitors target the viral neuraminidase protein and should not be described as polymerase inhibitors. Recent evidence from randomised trials supports the continued role of direct-acting antivirals in severe influenza, although evidence certainty varies by outcome and treatment [24].

For RSV, antiviral development has focused on viral fusion and replication mechanisms. Several candidate small molecules and monoclonal antibodies have reached clinical development [3].

For SARS-CoV-2, antiviral therapy is most relevant during the phase in which viral replication contributes substantially to disease. Post-acute inflammatory symptoms do not automatically imply that continued antiviral treatment will address the underlying mechanism.

13.2. Immunomodulation

Immunomodulatory therapy may be useful when excessive host inflammation contributes substantially to tissue damage. However, immune suppression during active viral replication may theoretically interfere with antiviral defence.

The challenge is therefore to identify the disease stage before selecting a target.

Potential targets include IL-1, IL-6, JAK/STAT signalling, inflammasomes, and other inflammatory pathways. At present, evidence for many interventions aimed specifically at persistent post-viral inflammation remains limited.

13.3. Antioxidant and mitochondrial approaches

Mitochondrial dysfunction and oxidative stress are attractive therapeutic targets because they sit at the centre of cellular metabolism, inflammatory signalling, and cell death [21].

However, most proposed mitochondrial therapies remain experimental or are supported by evidence from conditions broader than respiratory viral infection.

13.4. Antifibrotic and tissue-repair approaches

Patients with established structural remodelling or fibrosis may require a different therapeutic strategy than patients with active viral replication.

Fibrotic disease involves complex interactions between epithelial injury, inflammatory cells, fibroblasts, TGF- β signalling, and extracellular matrix production [23]. Consequently, future therapies may need to target repair and remodelling rather than viral replication itself.

Table 2. Potential therapeutic strategies according to disease stage

Disease stage	Potential target	Therapeutic concept	Current evidence	Major limitation
Active viral replication	Viral polymerase, protease, neuraminidase, fusion machinery	Direct antiviral therapy	Strong for selected viruses	Time-dependent efficacy and resistance
Acute excessive inflammation	Cytokine and inflammatory pathways	Targeted immunomodulation	Virus- and disease-specific	Risk of impairing antiviral immunity
Persistent inflammation	IL-1/IL-6/JAK and related pathways	Host-directed therapy	Emerging	Limited evidence for post-viral disease
Oxidative/mitochondrial stress	ROS, mitochondrial dysfunction, mitophagy	Metabolic/mitochondrial modulation	Mainly experimental	Limited clinical validation
Airway remodeling	Smooth muscle/fibroblast and ECM pathways	Remodelling-directed therapy	Emerging	Mechanisms differ among diseases
Fibrosis	TGF- β and fibrotic pathways	Antifibrotic therapy	Established in selected fibrotic diseases; virus-specific evidence limited	Patient selection and reversibility

14. Knowledge Gaps and Future Directions

Several important questions remain unresolved.

First, we need to understand better the difference between viral persistence and post-infectious immune dysregulation. Viral RNA/antigen presence does not necessarily indicate replication-competent virus. Future research should separate residual nucleic acids, persistent antigen,

replication-competent virus and immune responses that continue in the absence of viral replication [9,10].

Second, more longitudinal studies are needed. Cross-sectional studies cannot always determine whether the inflammatory abnormality resulted from the original severity of infection or led to persistent symptoms.

Third, the concept of ‘epithelial memory’ needs further exploration. Recent experimental studies indicate that respiratory virus infection may affect progenitor cell behaviour following acute infection [7,17]. It remains unknown whether similar changes occur in humans and whether they foreshadow the development of long-term respiratory disease.

Fourth, the evidence base is far less uniform for viruses. Evidence for post-acute disease after rhinovirus or adenovirus infection is more context-dependent, whereas a large body of human research exists on SARS-CoV-2, the cause of COVID-19.

Fifth, interpret animal and cell culture models with caution. They help elucidate mechanisms but are not always as complex as human respiratory illness.

Last, future trials should consider disease staging. Patients with ongoing viral replication, patients with ongoing inflammation after viral clearance, and patients with established pulmonary fibrosis may have different pathophysiological mechanisms and thus require different treatments.

15. Limitations of the Evidence

This narrative review has several limitations. The available literature is heterogeneous in several respects, including virus species, patients studied, disease severity, the definition of persistence, and experimental models.

Second, many molecular mechanisms are supported mainly by in vitro or animal studies. This helps establish biological plausibility and should NOT be viewed as evidence of clinical causation.

Third, viral persistence is best documented for SARS-CoV-2. It’s less clear how much these mechanisms contribute to long-term disease following influenza, RSV, rhinovirus, or adenovirus infection.

Fourth, several different biological conditions are associated with the term “chronic inflammation.” It is important to remember that the four categories of cytokine production, recurrent airway inflammation, tissue remodelling and fibrosis, and post-viral symptoms are not synonymous.

The constraints highlight the importance of well-designed longitudinal studies that incorporate clinical phenotyping and molecular and cell-based assays.

16. Conclusions

A simple return to pre-infection life is not always achieved following a respiratory viral infection. While most people will recover without a long-term disease, some will experience long-term inflammation, dysfunction or abnormalities. Evidence suggests these effects can result from interactions between viral signals, innate immune activation, epithelial damage,

metabolic/mitochondrial dysfunction, inflammatory cell death, changes in cell-cell communication, and abnormal tissue repair.

Many examples of post-acute disease and potential SARS-CoV-2 persistence exist, but the same principles apply to other infections such as influenza, RSV, rhinovirus, and adenovirus. Importantly, these viruses do not share the same mechanisms. Rhinovirus is strongly associated with recurrent airway inflammation and remodelling; RSV can drive long-term changes in epithelial responses; influenza can influence repair after substantial tissue injury; and adenovirus can cause severe immune-mediated pulmonary injury and persistent infection in selected hosts [5,7,11,12].

The therapeutic implications are also crucial. Active viral replication and post-viral inflammation represent two distinct states of the biological system. Direct antiviral treatment applies when the virus is actively replicating. In contrast, host-directed or tissue-directed treatment may be indicated if there is a persistent inflammatory signature, disrupted tissue repair, or fibrotic disease.

The future of this field will depend on determining which mechanisms are engaged in each patient, rather than assuming that the same mechanism causes all long-lasting respiratory symptoms. These complementary technologies—such as longitudinal clinical studies, single-cell transcriptomics, spatial biology, proteomics, metabolomics, and detailed immune phenotyping—may provide the basis for defining clinically meaningful subgroups and developing targeted therapeutics for each disease stage.

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