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Review

The Role of the Nrf2 Pathway in Airway Tissue Damage Due to Viral Respiratory Infections

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Abstract: Respiratory viruses constitute a significant cause of illness and death worldwide. Respiratory virus-associated injuries include oxidative stress, ferroptosis, inflammation, pyroptosis, apoptosis, fibrosis, autoimmunity, and vascular injury. Several studies have demonstrated the involvement of the nuclear factor erythroid 2-related factor 2 (Nrf2) in the pathophysiology of viral infection and associated complications. It has thus emerged as a pivotal player in cellular defense mechanisms against such damage. Here, we discuss the impact of Nrf2 activation on airway injuries induced by respiratory viruses, including viruses, coronaviruses, rhinoviruses, and respiratory syncytial viruses. The inhibition or deregulation of Nrf2 pathway activation induces airway tissue damage in the presence of viral respiratory infections. In contrast, Nrf2 pathway activation demonstrates protection against tissue and organ injuries. Clinical trials involving Nrf2 agonists are needed to define the effect of Nrf2 therapeutics on airway tissues and organs damaged by viral respiratory infections.

Keywords: respiratory virus; Nrf2; virus-induced injury; lung injury; inflammation; pyroptosis; apoptosis; ferroptosis; fibrosis; autoimmunity; oxidative stress

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1. Introduction

Respiratory viral infections, such as influenza and coronavirus disease 2019 (COVID-19), cause significant mortality and morbidity worldwide. Respiratory viruses (RVs) commonly affect respiratory tract airways. They are classified as upper respiratory tract infection (URTI)-associated injuries, which are commonly mild and transient, and lower respiratory tract infection (LRTI)-related injuries, which are commonly severe and associated with chronic diseases and mortality. Up to 70% of pneumonia cases are attributed to viral infections [1–3]. Acute respiratory distress syndrome (ARDS) is characterized by diffuse lung inflammation and edema, hypoxemia, and acute respiratory failure and is commonly caused by viral pneumonia. Of note, more than 4 million deaths are attributed to virus-induced LRTI-associated injuries [4].

The RVs that cause ARDS-induced pneumonia include severe acute respiratory syndrome (SARS)-CoV (2002) [5], H5N1 and H1N1 influenza viruses (2009) [5,6], MERS-CoV (2012), and SARS-CoV-2 (2019) [7,8], which is the leading cause of the COVID-19 pandemic. Furthermore, other lower respiratory tract infections, including bronchitis and bronchiolitis, are caused by RVs, especially respiratory syncytial viruses (RSVs), influenza viruses (IVs), parainfluenza (PIV), and adenoviruses, which are more diagnosed in children and infants with bronchitis and bronchiolitis [9,10]. Human rhinoviruses (HRVs), PIVs, RVS, CoVs, adenoviruses, and IVs are the predominant etiological agents of upper respiratory tract infections (URTIs). Several host factors drive viral-induced tissue damage during respiratory viral infections. However, it remains unclear how RVs interact with host tissue responses.

During infection, RVs induce the generation of reactive oxygen and nitrogen species (ROS and RNS), which disrupt redox homeostasis and subsequently lead to oxidative stress [11,12]. Viruses that induce prooxidant cellular responses include (hMPV) [13], HRVs [14–17], enteroviruses (EVs, including EV-71 and Coxsackievirus B3 [18–20] CoVs [21–29], RSVs [13,30–42], IVs [43–50], and PIVs [51,52]. Increased viral-induced oxidative stress then compromises the infected host cells through different molecular and cellular structure damages and increased viral replication, altering the function of organs and the immune response field [12,53,54]. Of note, increased redox stress is the main leading cause of respiratory virus-induced injuries and diseases. To clear viral infection(s) and reestablish cellular redox balance, the host deploys a solid and specific antiviral response, especially the antioxidant host response, which is mainly modulated by the activated nuclear factor erythroid 2-related factor 2 (Nrf2) pathway.

Nrf2 is a protein capable of binding to the nuclear factor, the erythroid-derived 2/activator protein 1 (NF-E2/AP1) repeat of the beta-globin gene [55]. After discovering its beneficial role in regulating the expression of many antioxidant and detoxification enzymes, including heme oxygenase-1 (HO-1) and glutathione S-transferases (GSTs), Nrf2 became the target and center of extensive research. Since then, it has been demonstrated that Nrf2 regulates balance and maintains the homeostasis of the cellular redox system by controlling the production level of ROS and the activation of antioxidant immune molecules (HO-1 and GSTs). Specifically, antioxidant treatments [37] and host-secreted cytosolic HO-1 and GSTs have been associated with a relevant decrease in respiratory viral-associated oxidative stress-induced cell damage and anti-inflammatory and anti-apoptotic properties [47,56–58], which soothe respiratory virus-associated infections and damage and attenuates complications (Figure 1).

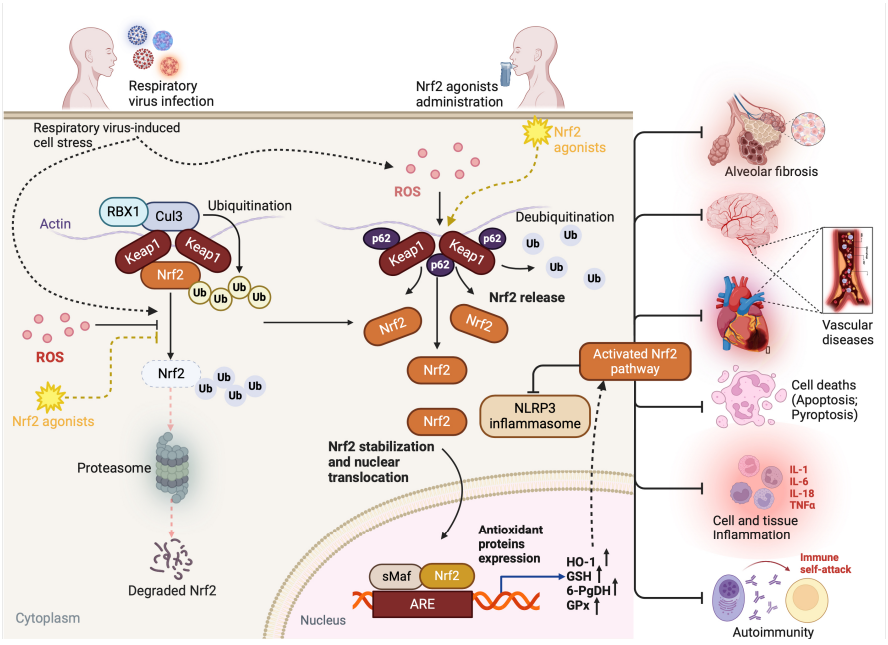


Figure 1. The role of the Nrf2 pathway in airway injuries due to viral respiratory infections. Viral respiratory infections are one of the main leading causes of airway damage. Respiratory virus-associated injuries include oxidative stress, ferroptosis, inflammation, pyroptosis, apoptosis, fibrosis, autoimmunity, and vascular injury. The inhibition or deregulation of Nrf2 pathway activation induces airway tissue damage in viral respiratory infections. The inhibition or downregulation of the Nrf2 pathway can be rescued by Nrf2 agonists that boost the activation of Nrf2. (Created with BioRender.com, 2024, accessed on 12 June 2024).

As we recently reviewed, the Nrf2 pathway also plays an essential role in the replication of respiratory viruses and helps to restore disrupted redox homeostasis. However, the way in which viral replication interacts with the Nrf2 pathway is complex since RVs

can leverage the Nrf2 pathway for their replication. Independent of the effects on viral replication, Nrf2 may play protective roles in cell and tissue damages induced by RVs [45]. Non-exhaustively, the cell tissues and organs affected in viral pathogenesis include the pharynx, larynx, trachea, and, most importantly, lung cells and tissues, for which severe damage is associated with respiratory distress and life-threatening pathologies. However, the role of Nrf2 pathways in cell and tissue damage remains unclear since both the down-regulation/inhibition or upregulation/hyper-activation of this pathway can have complex effects on several host pathways that include but are not limited to cell inflammation, apoptosis, ferroptosis, fibrosis, vascular dysfunction, and autoimmunity [59–62]. Herein, we review the scientific evidence regarding the critical role of the Nrf2 pathway in the pathogenesis of end-organ airway tissue damage associated with RVs with a focus on common viruses such as HRVs, RSVs, IVs, and CoVs (SARS-CoV-2). Understanding host pathways mediating virus-induced tissue damage may lead to the development of novel therapies for airway damage induced by viral respiratory diseases.

2. The Nrf2 Pathway

Activating NRF2 enables cells to adapt to stress reactions and maintain redox balance. Mechanistically, Nrf2 is first synthesized in the cytoplasm and then combines with Keap1 through the Neh2 domain of Nrf2 that can recognize different sites in Keap1 and form the disulfide-bounded Nrf2-Keap1 complex [63,64].

Without triggers or infection, the Nrf2 signaling cascade remains inactive. In the Nrf2-Keap1 complex, cysteine residue contributes to the transfer of dipeptide derivatives, enabling the ubiquitination and degradation of Nrf2 through the proteasome signaling pathway, which actively processes to maintain Nrf2 at a low cytoplasmic level (Figure 1).

Several signaling cascades have been proven to activate the Nrf2 pathway under stress, including the p239/MDM2 pathway, which requires a complex collaboration to allow for the normal activation of Nrf2. However, upon infection, cells produce enough harmful factors, which trigger a series of reactions, causing excessive cytosolic ROS and RNS production and specifically inducing the disruption of the internal balance of oxidation and antioxidants (redox homeostasis). Notably, during infection, the synthesis levels of superoxide ($O_2^{\bullet -}$)-, hydroxyl ($HO^{\bullet}$)-, peroxyl ($RO^{\bullet -2}$)-, and hydroperoxyl ($HO^{\bullet 2}$)-derived ROS, nitric oxide (NO)-derived RNS, the transcription of the inducible NO synthase (iNOS) gene, and the phosphorylation of STAT-1 significantly increase as they are beneficial for host defense mechanisms and pathogen clearance [65–67]. However, because of the cytotoxicity of these molecules for tissues and organs, in abnormally high concentrations, they may induce inflammation, allergic and autoimmune diseases, and multiple types of damage in the airways when they are not well regulated or upon persistence of the infection [65,66]. Thus, under these infection-induced stress conditions, Keap1 undergoes oxidative modification, leading to a conformational change in the shape of the Keap1-Nrf2 complex, releasing Nrf2 from Keap1, which accumulates in the cytoplasm. Cytosolic accumulated Nrf2 translocates into the nucleus and then binds to the antioxidant response element (ARE) to initiate the transcription of various cytoprotective genes (Figure 1).

When Nrf2 reaches the nucleus, it activates the production of ROS-quenching genes to rebalance the production and scavenging of ROS. These stressors induce the production of a group of cytoprotective antioxidant enzymes, including HO-1, NAD(P)H quinone oxidoreductase 1 (NQO1), superoxide dismutases (SOD), catalase, glutathione peroxidase (GPx), glutathione reductase, GST, thioredoxins, γ-glutamyl-cysteine ligase (γ-GCL), and many isoforms of aldo-keto reductases, by using Nrf2 to recognize the ARE promoter (Figure 1) [68,69]. The number of NRF2-regulated genes is extensive and includes the most protective antioxidants, Phase II detoxifying enzymes, and many drug influx/efflux transporters that can serve to eliminate both endogenous and exogenous toxic products [68,70].

This activation of the Nrf2 signaling cascade is crucial in establishing cell redox homeostasis, defense against RVs, and the pathogenesis of related respiratory diseases. As we recently reviewed, the activated Nrf2 pathway also plays an essential role in the

replication of respiratory viruses. Herein, we will review the scientific evidence regarding the role of the Nrf2 pathway in respiratory virus-induced oxidative stress and ferroptosis, inflammation and pyroptosis, apoptosis, fibrosis, autoimmunity, and vascular injury, which collectively drive tissue damage and end-organ disease.

3. The Role of the Nrf2 Pathway in Respiratory Virus-Induced Oxidative Stress and Ferroptosis

As outlined above, oxidative stress has a significant role in the pathogenesis of respiratory viral infections. One aspect important for redox-related pathogenesis is ferroptosis, a programmed and regulated cell death mechanism used by host cells to clear infections by pathogens, including RVs. Discovered a decade ago and unlike other programmed cell deaths, ferroptosis is an exclusively iron-dependent process characterized and induced by the excessive production and accumulation of iron-mediated ROS and lipid peroxides [71]. Ferroptosis cell death differs from autophagy and other programmed cell deaths, such as apoptosis and pyroptosis, at different levels, including at the morphological, biochemical, and genetic levels (reviewed in [71]). Infections with RVs have been associated with several pathophysiological signatures of ferroptosis that drive respiratory tissue and organ damage, including the disruption of the cell redox homeostasis and depletion of glutathione peroxidase 4 (GPX4) and antioxidant glutathione (GSH) (Table 1) [72–90].

Table 1. Impact of respiratory viruses on redox and ferroptosis pathways.

Viruses	Impact on Ferroptosis	Reference
Influenza	• ↓ in cellular concentration of GSH and/or ↓ in GPX4 activity and ↓ in redox state and normal antioxidant response have been reported in infections with IVs (IAV, swine influenza virus)	[73–77]
	• Typical changes in iron metabolism, lipid peroxidation, selenoprotein and GSH levels, and mitochondrial and lysosomal activity have been associated with severity of influenza infections	[75–78]
SARS-CoV-2	• ↑ in oxidative stress, which plays a major role in SARS-CoV-2 infection-induced multiple organ failure	[78]
	• ↑ in iron metabolism dysfunction	[79,80]
	• ↑ in production of lipid peroxidation markers, such as oxidized phospholipids and 4-hydroxynonenal (HNE)	[81,82]
	• ↑ in acyl-CoA synthetase long-chain family member 4 (ACSL4)	[83]
	• ↓ in levels of L-cysteine (a rate-limiting precursor of GSH)	[84–89]
	• ↓ in GSH correlating with ↓ in vitamin D binding protein (VDBP) and VD levels; ↑ in ROS and oxidative stress levels	[78]
	• COVID-19 patients show imbalanced iron metabolism causing increased ferritin concentration in blood, which is transferred into cells by TfR1 (transferrin receptor 1), activating Fenton reaction	[78]
RSV	• Study on RSV-infected mice described ↑ secretion of pro-inflammatory chemokines CCL5 and CCL3 and ↑ expression of mitochondrial iron content and 12/15-lipoxygenase (12/15-LOX, ↑ deoxygenation of poly unsaturated fatty acids), which correlated with ↑ in 12/15-LOX signaling pathway	[90]
Enterovirus	• During enterovirus infections, Coxsackie virus causes ↑ in serum iron intake from gastrointestinal track, which results in ↑ in typical cellular oxidative stress that damages myocardium of mouse models	[78,91,92]

Abbreviations: IAV: influenza A virus, ROS: reactive oxygen species, RSV: respiratory syncytial virus.

Nrf2 transcriptionally regulates most of the genes involved in ferroptosis, such as GPX4 [93–95] (Figure 2). Recently, different RVs have been shown to inhibit ferroptosis by inducing Nrf2 degradation. H1N1 virus infection caused the differential expression of

many ferroptosis-related genes and metabolites in human nasal mucosal epithelial cells by suppressing the expression of the glutamate-cysteine ligase catalytic (GCLC) subunit via the Nrf2 -KEAP1 pathway [96]. Tripartite motif-containing protein 21 (TRIM21) has been shown to physically interact with SQSTM1 and Nrf2 -KEAP1 and mediates Nrf2 degradation to induce oxidative stress and ferroptosis during pathogenic avian IV H5N1 infection [97]. Pyrogallol, a natural polyphenol compound (1,2,3-trihydroxybenzene), promoted the expression and nuclear translocation of Nrf2 and alleviated influenza A disease in human alveolar epithelial cells and mice [98]. When SARS-COV2 spike protein was overexpressed in HEK293 cells, Nrf2 showed an upregulation of Nrf2 in the presence of palmitic acid (PA) overload [99]. SARS-CoV-2 ORF3a promotes the degradation of Nrf2 through recruiting Keap1, thereby attenuating cellular resistance to oxidative stress and facilitating cells to ferroptotic cell death [100,101]. These data suggest that the cross-talk between the Nrf2 pathway and ferroptosis is essential for the pathogenesis of viral respiratory infections [102].

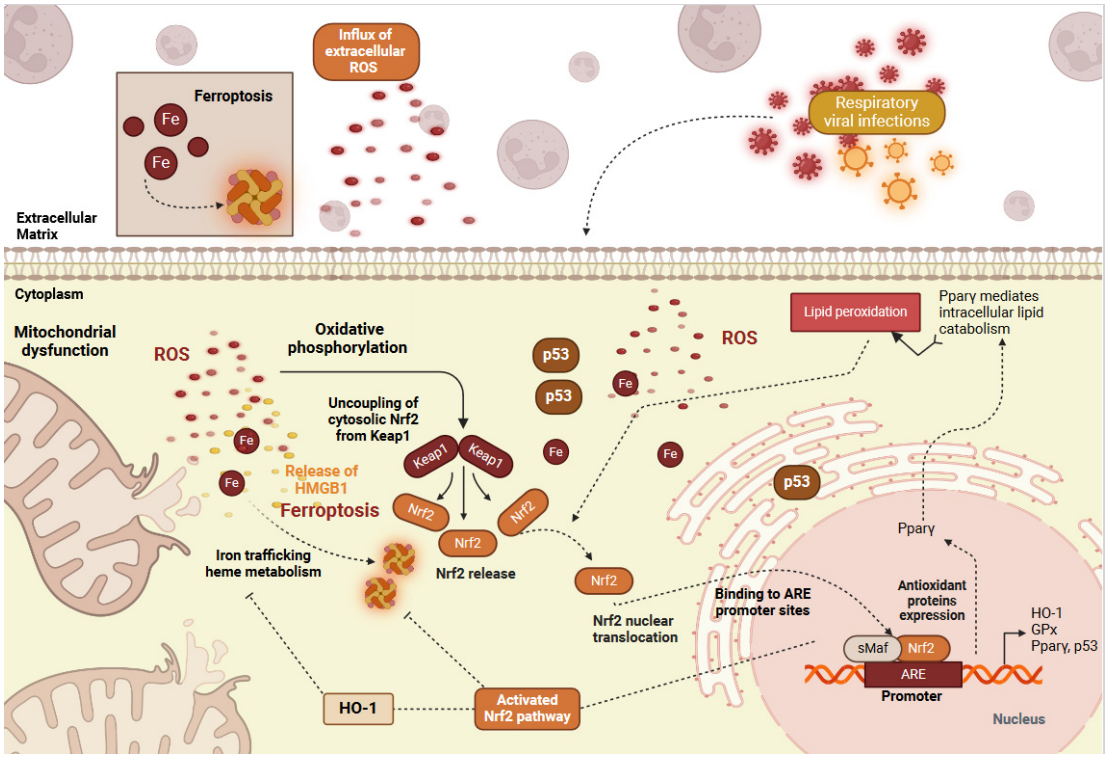


Figure 2. The cross-talk between the Nrf2 pathway, oxidative stress, and ferroptosis in viral respiratory infections. Networks behind the formation of ferroptosis and subsequent Nrf2 activation during viral respiratory infections. Ferroptosis is primarily characterized by iron (Fe) accumulation and the formation of iron complexes. Iron and ROS accumulation sensitize the cellular membrane to exhibit PPARγ-mediated lipid peroxidation, thereby activating Nrf2. The activation of the Nrf2 pathway inhibits ferroptosis through the transcription of heme-oxygenase enzyme HO-1 and glutathione synthesis enzymes GPx and Gclc, as well as the regulation of p53 and PPARγ. Increased cytosolic HMGB1, ROS, and iron concentrations also lead to mitochondrial dysfunction. ROS, reactive oxygen species; GSH, reduced glutathione; GSSG, oxidized glutathione; GPx, glutathione peroxidase; Nrf2, nuclear factor erythroid 2-like factor 2; Keap1, Kelch-like ECH-associated protein 1; Pparγ, peroxisome proliferator-activated receptor gamma; HMGB1, high mobility group box 1; HO-1, heme-oxygenase-1; Gclc, γ-glutamyl cysteine ligase; ARE, antioxidant response element. (Created with BioRender.com, 2024, accessed on 12 June 2024).

4. The Role of the Nrf2 Pathway in Respiratory Virus-Induced Inflammation and Pyroptosis

The airway epithelium consists of the large physical inner body surface barrier that directly interacts with and senses antigens and infectious agents to initiate immune responses. The immune response is triggered to clear the infection, but the whole mechanism requires the epithelium to undergo injuries (at least minor) characterized by epithelial cell inflammation and death. Even though the lower airway cells and tissues are sites where inflammations occur in most respiratory viral infections, the upper airway remains the first point of contact with RVs, and thus, the prime site of tissue inflammation, such as sinusitis, laryngitis, pharyngitis, and, ultimately, lung inflammation. Mechanistically, upon active respiratory viral infection, viral particles infiltrate the upper airways and spread across the lower airway epithelial cells, triggering the host's innate and adaptive immune responses. In immunocompetent people with healthy airway tracts, tissue inflammation and the pyroptosis of immune cells are beneficial and transient due to a robust and highly regulated type 1 inflammatory response, which leads to a clearance of the respiratory viral infection [103,104]. However, in people with unhealthy airways and compromised health conditions, the inflammatory response may be impaired and inefficient, exacerbating the viral replication and enhancement of the immune cell infiltration and lung disease [105]. Thus, short-term airway inflammation contributes to viral clearance and the healing process [59–61,106], while sustained inflammation is associated with severe injuries and the immunopathology of viral infection in airway tissues (Table 2).

Table 2. Impact of respiratory viruses on inflammation and pyroptosis.

Viruses	Mechanism of Inflammation	Reference
Common respiratory viruses (RSV, HRV, CoVs, IVs, Other viruses)	• ↑ pro-inflammatory cytokines, and chemokines induced by myeloid cells that alter local airway niche and activate immune and non-immune cell inflammation. • ↑ Type I (IFNα/β) and type III (IFNλ) interferons, interleukins (IL)-6, IL-8, IL-12, RANTES, macrophages-associated inflammatory protein 1α and monocytes-associated chemotactic protein 1, in host epithelial cells.	[105–121]
	• ↑ innate immune cell infiltration, responsible for production of type II interferon (IFNγ), IL-2, IL-4, IL-5, IL-9, and IL-12.	[105]
	• ↑ redox-mediated inflammasome activation → ↑ caspase-1, → ↑ cleavage of gasdermin D (GSDMD) → ↑ regulated form of cell death called pyroptosis → DNA fragmentation and rapid plasma membrane permeability. • ↑ IL-1b, IL-18 → ↑ leukocyte innate immune cell infiltration • ↑ inflammasome activation, including NLRP3 (CoVs, PIVs, and IVs). • In asthmatic patients infected with HRV and RSV, the activated Th2 immune response is biased and ↑ production of IL-4, IL-5, IL-13, RANTES and eotaxin and ↑ in eosinophilic infiltration.	[106,109–123]
	• ↑ phosphorylation of the redox-sensitive PKC ↑ NRF2 dissociation from KEAP1.	[21,36,43]
Influenza	• ↑ pyroptosis-related respiratory epithelium damage	[106,108,109,124,125]
	• ↑ proinflammatory responses in endothelial cells and damage in epithelial-endothelial tight junctions	[108,126]
SARS-CoV-2	• ↑ epithelial cell inflammation, which is a central cause of lung tissue damage and COVID-19 severity	[22,23,25,27,62,101,120,121,127,128]
	• ↑ caspase-1, → ↑ cleavage of gasdermin D (GSDMD) → regulated form of cell death called pyroptosis → DNA fragmentation and rapid plasma membrane permeability.	[120,121,123,129,130]
RSV	• ↑ viral bronchiolitis and pneumonia in infants and children	[30,34,35]

Abbreviations: RSV: respiratory syncytial virus, HRV: human rhinovirus, CoVs: coronaviruses, IVs: Influenza viruses.

Known to regulate and maintain redox homeostasis, Nrf2 also significantly influences inflammation through various mechanisms (Figure 3). The activation of Nrf2 has been shown to trigger an anti-inflammatory response and concomitantly inhibit the upregulation of pro-inflammatory cytokines like IL-6, IL-18, and IL-1β, likely through interference with NF-κB-mediated transcription [131]. This regulatory role extends to other inflammatory mediators, such as chemokines and cell adhesion molecules (CAMs), which are crucial for leukocyte recruitment and tissue inflammation and damage [132]. Moreover, Nrf2 influences the balance between proteases and antiproteases, thus modulating tissue remodeling and inflammatory responses. Additionally, Nrf2 signaling interacts with matrix metalloproteinases (MMPs), enzymes involved in extracellular matrix degradation, and (COX), which catalyze the formation of pro-inflammatory prostaglandins. The activation of Nrf2 has been linked to the suppression of MMPs and COX-2 expression, contributing to the resolution of inflammation [132]. Experimental evidence demonstrates that Nrf2-controlled HO-1 induction leads to anti-inflammatory effects, such as increased IL-10 release in M2 macrophages and the attenuation of inflammation in various RV-induced pathological conditions [132]. Furthermore, studies showed that Nrf2 activation suppresses the expression of pro-inflammatory proteins and cytokines like cyclooxygenases (COX-2), iNOS, TNF-α, IFN-γ, and IL-6. For instance, in Nrf2-deficient mice models, inflammatory responses were exacerbated [133].

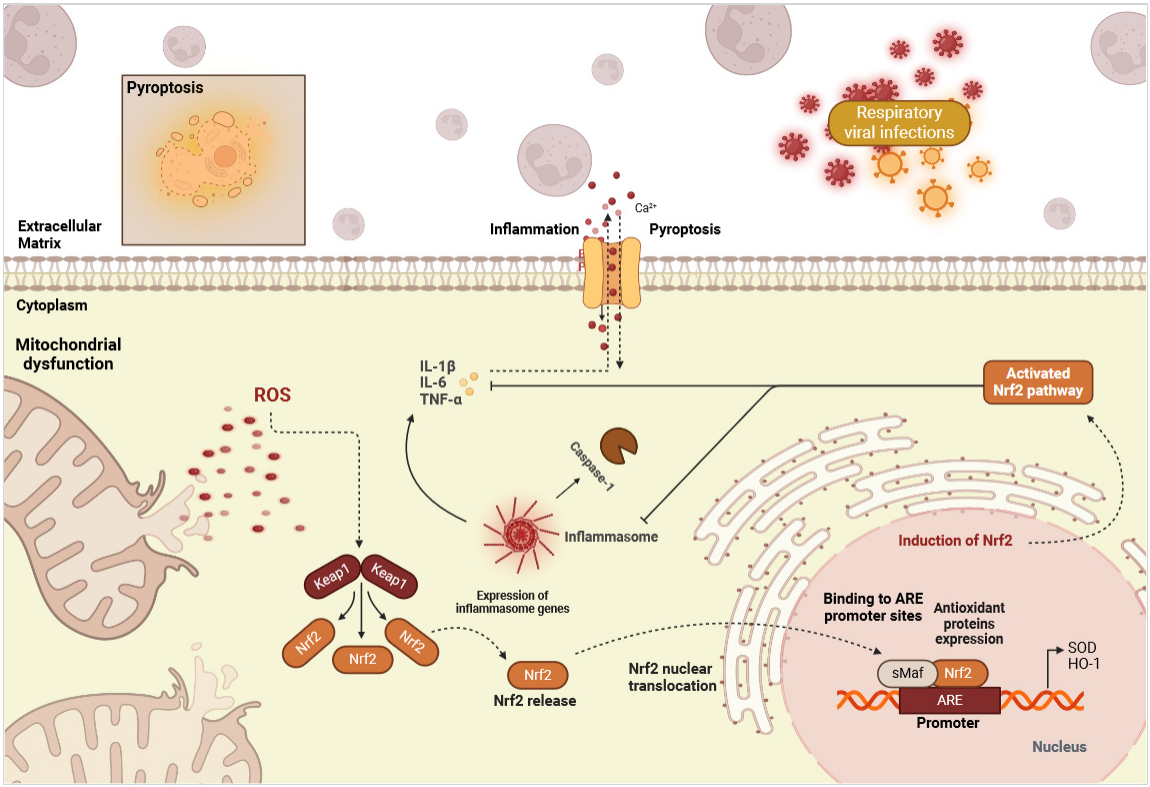


Figure 3. The cross-talk between the Nrf2 pathway, inflammation, and pyroptosis in viral respiratory infections. Antioxidant products increase Nrf2 activity, attenuating ROS production and preventing NF-kB oxidation. Some amino acid residues are oxidized in these compounds for inflammasome activation and pyroptosis induction. (Created with BioRender.com, 2024, accessed on 12 June 2024).

Notably, in IV infections, Nrf2 activation reduces NF-κB-mediated inflammation and the associated lung permeability damage and mucus hypersecretion [48–50]. Interestingly, the protective effects of Nrf2 seem to extend to resolving inflammation in influenza-induced chronic airway inflammation [132,134,135]. RSV-induced bronchopulmonary epithelial injury and inflammation were higher in Nrf2 knock-out mice than in the control $Nrf2^{+/+}$ mice. Nrf2 knock-out mice infected with RSV had reduced viral clearance, low IFN-

gamma levels, decreased body weights, and dysregulated antioxidant activity [39–42,131]. Moreover, as inflammation is modulated by NLRP inflammasomes [136], the masterpiece of pyroptosis activation (Figure 3), pretreatment with sulforaphane or viroporin prevents NLRP3 inflammasome activation and significantly limits lung RSV/rhinovirus replication and NLRP3-induced inflammation in control $Nrf2^{+/+}$ but not in Nrf2 knock-out mice, suggesting the pivotal role of Nrf2 in controlling virus infection [17,39,49] and specifically by hampering NLRP3 activation and associated inflammation [39–42,131,133]. This is also true in CoVs (SARS-CoV-2), rhinovirus, enterovirus 71, and metapneumovirus infections, where infected transgenic $Nrf2^{-/-}$ or $Keap1^{-/-}$ mice display antioxidant enzyme depletion, increased K^+ efflux, oxidative stress, and virus severity-induced airway damage compared with $Nrf2^{+/+}$ mice [13,18,26,28,29,137,138].

Taken together, Nrf2 exerts a multifaceted influence on inflammation and prevents aberrant and exacerbated inflammation by regulating various pathways and mediators involved in the inflammatory response. This intricate network highlights the therapeutic potential of targeting Nrf2 in inflammation associated with viral respiratory infections [33,139].

5. The Role of the Nrf2 Pathway in Apoptosis during Viral Respiratory Infections

Apoptosis is a physiologic process characterized by programmed cell death induced during reversible tissue expansion to control cell growth, replace unwanted old cells with new ones, and preserve tissues and organs [140]. Upon infection by viruses, for example, apoptosis is induced as a host-programmed death of virus-infected cells to fight viral infection. However, in most respiratory viral infections, apoptosis usually does not only serve as a protection mechanism for the host to eliminate the virus-infected cells but also, more commonly, promotes viral infection (Table 3).

Table 3. The impact of respiratory viruses on the apoptosis pathway.

Viruses	Impact on Apoptosis	Reference
Influenza	• Inflammatory response induced by IAV infection causes respiratory epithelial cell death (apoptosis) • In the initial infection phase, IAV ↑ viral products (genes and proteins) that ↓ the pro-apoptotic p53 pathway and ↑ the anti-apoptotic phosphoinositide-3-kinase-protein kinase B (PI3 K-AKT) pathway to ↓ apoptosis-based viral clearance • In the later phase of the infection IAV products ↓ the PI3 K-AKT pathway and ↑ the p53 pathway in order to abruptly lyse cells, spread the infection to neighbor cells and ↑ airway tissue damages • ↑ Fas expression • ↓ PKR and apoptosis • Apoptosis plays a role in viral release	[73,74,106,124,125,141,142]
SARS-CoV-2	• SARS-CoV-2 ↑ both intrinsic and extrinsic apoptosis pathway activation to escape antiviral immune response and promote its spread and survival.	[143,144]
	• Viral products involved in regulation of SARS-CoV-2 replication and apoptosis dysregulation include but not limited to ORF3α, ORF8, z-VAD-fmk, and CD95/Fas/APO-1.	[145]
	• SARS-CoV-2 ORF3α ↑ cleavage-based ↑ of caspase-8, known as a hallmark of the extrinsic apoptotic pathway and also in enhancement of cell death and tissue damage.	[146,147]
	• SARS-CoV-2 ORF3α knockdown fails to activate apoptosis and inhibit SARS-CoV-2-associated tissue injuries	[147]

Table 3. *Cont.*

Viruses	Impact on Apoptosis	Reference
RSV	• ↑ interferons and caspase 1	[73]
	• Experimental studies have shown that autophagy plays a very crucial role in RSV replication. • ↑ autophagy by ↑ the ROS-AMP-activated protein kinase/mammalian target of rapamycin (AMPK-MTOR) signaling pathway, which in turn ↑ cell apoptosis, responsible for immune cell infiltration, alveolar thickening, and hemorrhage in the lungs.	[148]
Adenoviruses	• ↑ apoptosis: ↑ sensitivity to TNFa that induces apoptosis, ↑ PP2A, ↑ p53 • ↓ apoptosis through several mechanisms: interacts with FADD ↓ CD95-mediated apoptosis, ↓ phospholipase A2, ↓ Fas, ↓ p53, ↓ pro-apoptotic proteins of the Bcl-2 family, such as Bax, Bak, BNIP3 and Bnip3L • ↓ apoptosis of the host cell in order to ↑ efficiently and the capacity of the virus to 'hijack' host cell apoptotic machinery	[73,74,149,150]
Rhinovirus, enteroviruses	• ↑ apoptosis through unknown mechanism	[73]
Coronaviruses	• ↑ apoptosis through ORF proteins and unknown mechanisms	[73]

Abbreviations: IAV: Influenza A virus, HO-1: ORF: Open Reading Frame, PKR: protein kinase R, p53: tumor protein 53, PP2A: Protein Phosphatase 2A, ROS: Reactive oxygen species, RSV: Respiratory syncytial virus, TNF-a: Tumor necrosis factor-alpha.

Notably, during infections with RVs, apoptosis has been associated with and characterized by prolonged respiratory epithelial cell and airway tract tissue injuries because RVs synthesize viral particles that dysregulate apoptosis and promote the lytic cell cycle.

Many reports demonstrated that the activated Nrf2 pathway plays a crucial role and has been shown to modulate apoptosis in a bidirectional manner (Figure 4). Nrf2 anti-apoptotic effects are mainly attributed to its ability to induce anti-apoptotic protein BCL2 transcription [151]. Nrf2 over-expression has also been shown to activate ERK1/2 and its downstream target, ELK1, suppressing IL-1β-induced apoptosis [152]. Nrf2 protects against H1N1 influenza virus-induced apoptosis in human alveolar epithelial cells [45]. Furthermore, Nrf2 activation has been reported to induce caspase-independent apoptosis and inhibit the growth of respiratory infections [153]. Sulforaphane is a naturally occurring isothiocyanate found in broccoli that has been shown to induce apoptosis via activating Nrf2 [154]. Isoliquiritigenin (ISL), a chalcone isolated from licorice (Glycyrrhizae Radix) root, is reported to be a natural Nrf2 agonist inhibiting H1N1, HSV-1, and EMCV replication in vitro [155]. Nrf2 activators have been reported to reduce SARS-COV2 viral pathogenesis by inducing the protease SPLI gene, anti-viral mediators such as RIG-1 and INFs, and by inhibiting anti-apoptotic proteins, TRMPSS2, and the NF-κB pathway [156]. Overall, this evidence highlights the role of the Nrf2 pathway in apoptosis during viral respiratory infections.

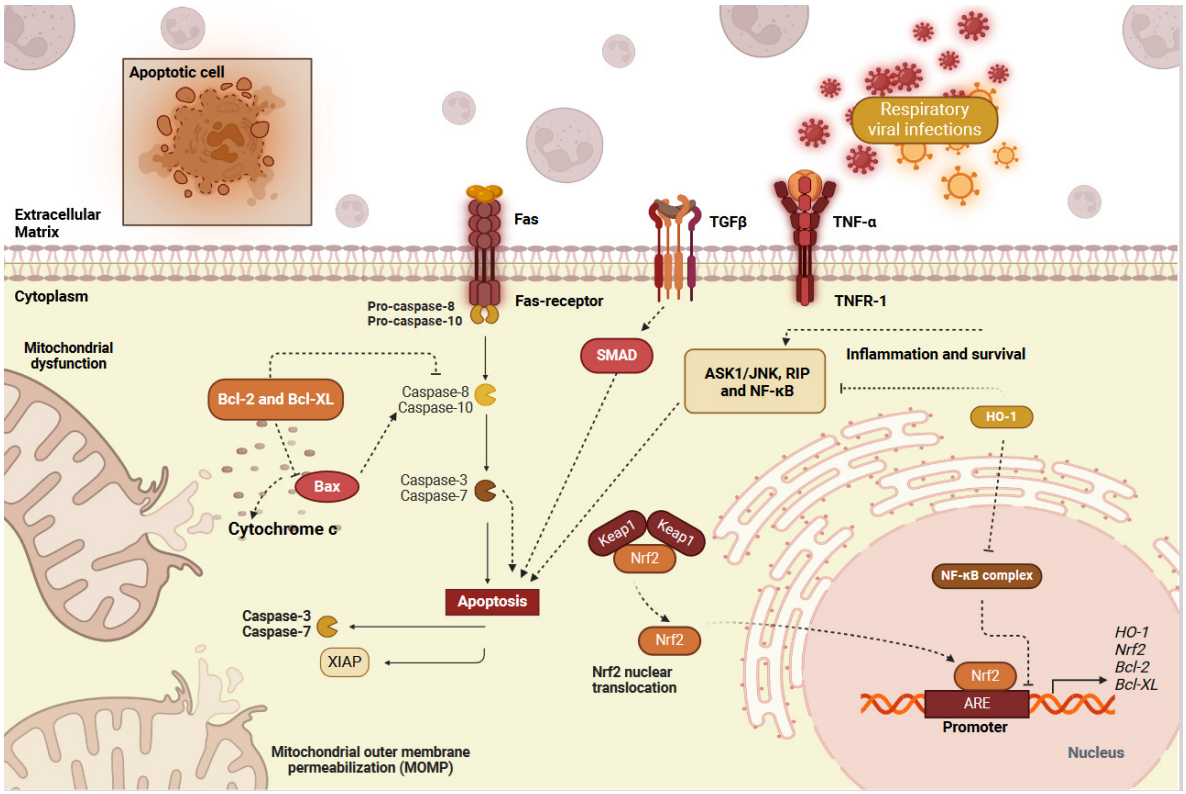


Figure 4. The cross-talk between the Nrf2 pathway and apoptosis in viral respiratory infections. The extrinsic induction of apoptosis occurs through cell surface receptor TGFβ, the downstream signaling of Smad, and the transduction of death domain receptors Fas and TNFα. Fas ligand binding to the receptor initiates the activity of cell execution molecules caspases 8/10, which subsequently activate pro-apoptotic caspases 3/7. Caspase 9 is an executioner molecule that intrinsically induces apoptosis and is activated by Bax-induced cytochrome c production. TNFα and downstream molecules transduce apoptotic signals, specifically ASK1/JNK, RIP, and NF-κB. The NF-κB complex hinders Nrf2 binding on promoter sites of target genes and repels it through Keap1 entry into the nucleus. As a response against apoptotic signaling, Nrf2 initiates the transcription of Bcl-2 and Bcl-XL to inhibit caspase signaling and HO-1 to limit NF-κB complex-mediated Nrf2 inactivation. TGFβ, tumor necrosis factor-beta; TNF-α, tumor necrosis factor-alpha; ASK1, apoptosis signal-regulating kinase 1; JNK, c-Jun N-terminal kinases; RIP, receptor-interacting protein; NF-κB, nuclear factor-κ of B cells; HO-1, heme-oxygenase-1; Bcl-2, B-cell lymphoma-2; Bcl-XL, B-cell lymphoma-extra-large; Bax, Bcl-2-associated X protein; Nrf2, atomic factor erythroid 2-like factor 2; Keap1, Kelch-like ECH-associated protein 1; ARE, antioxidant response element; Gclc, γ-glutamyl cysteine ligase. (Created with BioRender.com, 2024, accessed on 12 June 2024).

6. The Role of the Nrf2 Pathway in Respiratory Virus-Induced Fibrosis

Fibrosis refers to the development and excessive accumulation of fibrous tissues formed by extracellular matrix (ECM) component-producing myofibroblasts around inflamed or damaged tissue(s), leading to organ malfunctions and host death [157]. Although fibrosis may affect almost all tissues in the body [157], infections by RVs are most often associated with the development of only pulmonary fibrosis or idiopathic pulmonary fibrosis (IPF) [158–162]. Respiratory viral infections, such as influenza, coronavirus, and RSV have been associated with IPF and other severe complications (Table 4) [73,74,78,90–92,163–169].

Table 4. Impact of respiratory viruses on fibrosis pathways.

Viruses	Impact on Fibrosis	Reference
Respiratory viruses	• Severe chronic (but not acute) respiratory viral infections have been associated with IPF. • Acute respiratory viral infections may exacerbate/facilitate, or be exacerbated by pre-existing IPF condition, although the potential role of respiratory viral infection and the pathogenesis mechanism that leads to IPF remain elusive • respiratory viral infections ↑ a pathogenic chronic hyper-inflammatory response by ↑ ROS production and disrupting cell redox homeostasis • ↑ respiratory viral infections ↑ mitochondrial and endoplasmic reticulum stress are involved in the pathogenesis of IPF	[163–165]
Influenza	• 2009 H1N1 infection-induced ARDS, causes severe lung damage through an activated TGF-β/Smad pathway and ↑ endoplasmic reticulum stress, could promote IPF. • Avian influenza viruses (H7N9 and H5N1) are involved in the occurrence of pulmonary fibrosis • H1N1 ↑ TGF-β expression and activation of the Smad system • H5N1 ↑ TNF-α, FGF, and EGF, fibroblast proliferation, and collagen accumulation and ECM deposition	[73,74,166–168]
SARS-CoV-2	• More than 30% of patients who survived from severe COVID-19 pneumonia developed IPF six months after being discharged from the hospital • SARS-CoV and MERS-CoV outbreaks have been associated with substantial post viral fibrosis and physiological impairment. • CoVs (MERS-CoV and SARS-CoV) are involved in the occurrence of pulmonary fibrosis • CoVs ↑ pro-inflammatory cytokine storm and expression of type I/III collagen	[78,164,168,169]
RSV	• RSV infection promotes IPF through the unfolded protein response in a bleomycin-induced pulmonary fibrosis animal model	[90,165]
Enterovirus	• During enterovirus infections, Coxsackie virus ↑ serum iron intake from gastrointestinal track, which ↑ a typical cellular oxidative stress that damages the myocardium of mouse models	[78,91,92]

It has been reported that the deletion of Nrf2 in mice leads to decreased expression levels of antioxidant enzymes and phase II detoxifying enzymes, resulting in more severe bleomycin-induced inflammation and pulmonary fibrosis [170]. Overall, the activation of Nrf2 constitutes a protective mechanism against the promotion and progression of pulmonary fibrosis in respiratory viral infections by addressing multiple pathways involved in fibrosis pathogenesis, including oxidative stress, inflammation, Th1/Th2 balance, EMD, and EMT control (Figure 1). Given its protective functions, enhancing Nrf2 activity through pharmacological agents or dietary compounds holds a potential promise for preventing or treating pulmonary fibrosis, both generally and in the specific context of respiratory viral infections.

7. The Role of the Nrf2 Pathway in Autoimmunity Associated with Viral Respiratory Infections

Autoimmunity, also known as autoimmune disease (AID), occurs after a body's immune response loses self-antigen tolerance, causing the production of autoantibodies that attack the body's cells. Viral infections have been considered the major inducing factor, with respiratory viral infections contributing the most in triggering and exacerbating AID in genetically susceptible individuals (Table 5) [73,74,78,91,92,171–184].

Table 5. Impact of respiratory viruses on autoimmunity.

Viruses	Impact on Autoimmunity	Reference
Respiratory viruses	Mechanisms that mediate respiratory viruses-induced autoimmunity • Molecular mimicry • Bystander activation: respiratory viruses can cause significant and extensive tissue damage that leads to self-antigen release, which might activate autoreactive sentinel CD4+/CD8+ T-cells • Dysregulated immune response • Epitope spreading: during respiratory viral infections, immune response may expand to other specific antigen regions (that were not initially recognized), and lead to autoreactive T-cells and autoimmune response activation	[171–177]
Influenza	• IVs have been involved in the development of Guillain-Barré syndrome (GBS) and associated with molecular mimicry and bystander activation mechanism • IVs has been associated with development of type 1 diabetes (T1D) in genetically predisposed people	[73,74,178–184]
SARS-CoV-2	• CoVs including SARS-CoV-2, SARS-CoV, and MERS-CoV have been associated with several autoimmunity process including SLE, rheumatoid arthritis, and autoimmune thyroiditis through molecular mimicry, bystander activation, or dysregulated immune response	[78,185–188]
RSV	• RSV infection has been associated with development of type 1 diabetes (T1D) in genetically predisposed people	[90,179,181–184]
Enterovirus	• During enterovirus infections, Coxsackie virus ↑ serum iron intake from gastrointestinal track, which ↑ a typical cellular oxidative stress that damages the myocardium of mouse models	[78,91,92]

Notably, an AID induced by RVs and occurring in the airway system is known as an autoimmune respiratory disease (AIRD). Even though the mechanisms underlying the involvement of RVs in autoimmunity development are still elusive, at least four (4) pathogenic mechanisms, including molecular mimicry [171,172], bystander activation [172,173], dysregulated immune response [174,175], and epitope spreading, [176,177] have been unanimously proposed to explain respiratory virus-induced autoimmunity. The Nrf2 pathway has an established role in the pathogenesis of autoimmunity (Figure 1) [189,190]. The antioxidant and detoxification effects elicited by activating the Nrf2 signaling pathway may serve as a potential defensive mechanism against autoimmunity triggered by environmental pathogens, including RVs [191]. However, this area necessitates further research.

8. The Role of the Nrf2 Pathway in Vascular Injury during Viral Respiratory Infections

Respiratory viral infections have been listed among the highly morbid etiological risk factors associated with vascular disease. CoVs (SARS-CoV and SARS-CoV-2) and IVs are the main RVs related explicitly to vascular disease occurrence. It has been reported that COVID-19 patients of all ages are susceptible to undergoing virus-caused endothelial injury and dysfunction [192,193]. SARS-CoV-2 infection both exacerbates a preexisting vascular disease, such as coronary artery disease, and provokes the development of new pathological conditions in immunocompromised patients, such as venous thromboembolism. Similar to human studies, studies on infected animal models reported endothelial damage and vascular thrombosis in the lungs of rhesus macaques infected by SARS-CoV-2 [194]. It has been hypothesized that SARS-CoV-2 triggers the immune response and induces inflammation with the production of ROS, which can cause endothelial damage and dysfunction, impaired vasoregulation, increased permeability-associated vascular leakage, and coagulopathy, which is known to contribute to the development of vascular disease, such as vasculitis, thrombosis, and cardiovascular complications [192,195]. The dysregulation of

coagulation pathways and endothelial activation play crucial roles in SARS-CoV-2-induced thrombosis [196].

Armstrong et al. [197] reviewed the role of influenza in the exacerbation of vascular disease similar to SARS-CoV-2. Specifically, infection with IVs induces a pathogenic cytokine storm characterized by elevated cytokines and chemokines (TNF, IL-6, and IL-1β), which upregulate trypsin and result in the loss of the endothelial tight junction protein, zonula occludens-1 (ZO-1), and subsequent vascular hyperpermeability [197,198]. Moreover, a study on the H5N1 influenza strain reported that high and severe H1N1 infection induced elevated chemokine expression, causing endothelial barrier dysfunction and reversely endothelial activation, the loss of barrier function, and microvascular leakage, promoting the severity of the influenza infection. Additionally, several pieces of evidence demonstrate that IV-associated endothelial dysfunction is a risk factor for the occurrence of thrombotic events (reviewed in [197]).

Overall, RVs can induce vascular disease via mechanisms including the direct viral invasion of endothelial cells, the dysregulation of the immune response, and the activation of coagulation pathways.

The activation of the Nrf2 pathway also has anti-inflammatory effects on vascular tissues. Notably, Nrf2 activation suppresses the expression of pro-inflammatory cytokines and adhesion molecules, thereby attenuating endothelial dysfunction and vascular inflammation [199]. Additionally, Nrf2 activation can inhibit the nuclear factor-kappa B (NF-κB) signaling pathway, a central mediator of inflammation in vascular diseases [200,201]. The pharmacological activation of Nrf2 has been shown to attenuate oxidative damage, inhibit inflammation, improve endothelial function, and reduce atherosclerotic lesion formation in preclinical studies [200,202–204]. The Nrf2 pathway plays a significant role in protecting against vascular diseases induced by RVs by upregulating antioxidant and anti-inflammatory responses and promoting the transcription of cytoprotective genes, which restore vascular tissue homeostasis and protect against subsequent vascular damage (Figure 1).

9. Therapeutic Potential of Nrf2 Activation

As aforementioned and previously discussed [205], Nrf2 plays a crucial role in protecting against respiratory virus-induced injuries through its activation, as it upregulates antioxidant and anti-inflammatory genes, attenuates the replication of RVs (in most respiratory viral infections), and promotes airway tissue and organ repair (Figure 1). The inactivation or dysregulation of the Nrf2 pathway by viruses is associated with viral escape, the enhancement of oxidative stress and lipid peroxidation, and increased susceptibility to respiratory virus-induced injuries, which indicates that induced Nrf2 activation could be a potential therapeutic strategy in respiratory virus-induced injuries. Thus, to obtain the full therapeutic benefits of Nrf2 during respiratory viral infections and to prevent the virus-induced downregulation of Nrf2, researchers have focused on developing Nrf2 activators (known as Nrf2 agonists) and studying their efficacy (and safety) in preclinical and clinical studies (Table 6) [35,37,39,44,45,51,139,155,206–239].

Table 6. NRF2 agonists with protective effects in respiratory viruses-induced injuries.

NRF2 Agonists	Activity of Nrf2 Agonists in Respiratory Viruses-Induced Injuries	References
4-OI and derivatives	• ↓ replication of SARS-CoV-2 and IAV • ↓ Interferon responses and inflammation in IAV infection	[35,206–208]
DMF	• ↓ replication of SARS-CoV-2 • ↓ inflammation in SARS-CoV-2 infection	[35,206]
Curcumin	• ↓ replication of IVs, PIVs, and RSV • ↓ oxidative stress through HO-1 activation • ↓ inflammation and lung injury	[51,209–212]

Table 6. *Cont.*

NRF2 Agonists	Activity of Nrf2 Agonists in Respiratory Viruses-Induced Injuries	References
EGCG	• ↓ replication of SARS-CoV-2 and IVs through entry blockage • ↓ damages induced by respiratory viruses	[44,213]
Carbocistein	• ↓ TNF-α-induced airway inflammation through suppressing NF-κB and ERK1/2 MAPK pathways	[214,215]
BHBA	• ↓ RSV-induced oxidative stress • ↓ sodium arsenite (As(III))-induced cytoxicity in lung epithelial cells and prevent lung cancer	[139,216]
Sulforaphane	• ↓ hyperoxia-induced lung inflammation in neonatal mice • ↓ RSV, IAV, and SARS-CoV-2 replication and associated inflammatory cytokines • ↓ oxidative stress and respiratory viral replication • ↑ antifibrosis effects in IPF fibroblasts even under TGF-β stimulation • ↓ DEPs-stimulated inflammation in airway epithelial cells	[37,39,217–223]
tBHQ	• ↑ Nrf2 activation hampered by RSV • ↓ lung injury via regulating macrophage polarization and ARDS • ↑ pro- and anti-inflammatory balance	[31,218,224]
Resveratrol and Isoform γ-tocotrienol	• ↓ oxidative stress in the airway epithelium • ↓ LPS-induced ARDS • ↓ lung injury	[45,218,225–227]
CDDO-Im and its analogue	• ↓ lung injury in hyperoxia and aspiration-induced ARDS	[217,218]
Emodin, Quercetin, and Bitopertin	• ↑ antioxidant defense • ↑ inflammation and fibrotic lung injuries	[217,228–230]
Tempol and oligonol	• ↑ Nrf2-induce antioxidant defense and • ↓ viral replication and inflammation • ↓ ROS-associated injuries	[231–238]
Macrolides (Rapamycin, Metformin)	• ↑ expression of antioxidant proteins → ↓ ROS • ↓ resistance of lung adenocarcinoma	[239]
ISL	• ↓ H1N1, HSV-1, and EMCV replication and associated complication.	[155]

Abbreviations: ARDS: acute respiratory distress syndrome, IAV: Influenza A virus, IVs: Influenza viruses, PIVs: Para-Influenza viruses, BHA: Butylated hydroxyanisole, DMF: Dimethyl fumarate, EGCG: Epigallocatechin gallate, HO-1: Heme Oxygenase 1, IL-6: Interleukin 6, NRF2: Nuclear factor erythroid 2-related factor, 4-OI: 4-octyl itaconate, RSV: Respiratory Syncytial Virus, SARS-CoV-2: severe acute respiratory syndrome-coronavirus 2, tBHQ: tert-butylhydroquinone, ISL: Isoliquiritigenin.

Multiple therapeutic approaches targeting Nrf2 activation have been investigated in vitro and in vivo. Among the promising molecules for targeting the Nrf2 pathway, natural compounds are widely investigated because they combine the potential to modulate multiple targets simultaneously and due to their safety, availability, and affordability [240–245].

Most discovered and investigated activators have shown promising results in preclinical studies and hold great potential for treating RV infections and respiratory virus-induced injuries and complications (Table 6).

Sulforaphane has proven efficacy in reducing symptom severity associated with respiratory virus infections by activating the Nrf2 pathway, and it has also demonstrated positive outcomes in clinical trials. An advanced phase 4 clinical trial is ongoing to confirm the capability of sulforaphane as an Nrf2 activator in reducing respiratory virus replication and the associated complications in the general population. Similarly, curcumin and resveratrol have shown strong Nrf2 activating properties and have demonstrated potential

in epigallocatechin gallate. Specifically, curcumin has been demonstrated to inhibit the replication of RSV, influenza, and parainfluenza, thereby reducing the oxidative stress induced by viral infection, possibly via HO-1 activation. Resveratrol, on the other hand, has been found to inhibit the replication of RSV and decrease inflammation in the lungs through Nrf2 activation [205,246–251].

Dimethyl fumarate (DMF), an FDA-approved treatment for multiple sclerosis (MS) and psoriasis and a well-known Nrf2 activator, has also shown significant therapeutic potential as it displays an antiviral effect against SARS-CoV-2. Furthermore, DMF has been found to reduce inflammation, restore cell redox homeostasis, and improve lung function in respiratory SARS-CoV-2- and IAV-induced injuries, making it a promising candidate for future therapeutic interventions [25,35,206,252,253]. Bitopertin, a novel 7,7-dioxo-2-thioxo-3-bis(3-quinolinyl) isochromanyl sulfonamide medication used to promote the treatment of hypertension, counts among the promising Nrf2 activators. Current research indicates that bitopertin could reduce inflammation and enhance the body's defense against oxidative stress in the lungs of animals treated with bitopertin. As a result, these findings suggest that bitopertin may hold promise as a treatment for diseases primarily associated with a decrease in Nrf2, such as lung injuries caused by viruses [228–230]. Tempol, a well-known antioxidant agent that activates Nrf2, has been studied for its anti-inflammatory and antifibrotic effects using a mouse model that simulates stimulus-induced conditions. It has been discovered that intervention with Tempol can suppress the production of reactive oxygen species (ROS), inflammatory responses, and cell death and improve organ function [231–233,238].

Moreover, besides the cytoprotective effects of Nrf2 pathway activation, Nrf2 agonists may inhibit viral replication. Recently, Waqas et al. showed that Nrf2 agonists such as 4-octyl itaconate (4OI), bardoxolone methyl (BARD), sulforaphane (SFN), and the inhibitor of exportin-1 (XPO1)-mediated nuclear export selinexor (SEL) block IAV replication [254]. Similarly, as shown in Table 6, many other Nrf2 activators may interact with and prevent RV entry. The mechanism by which these agonists would block viral entry and replication remains unclear.

These findings suggest that these drugs could be a promising therapeutic option for treating respiratory virus-induced injuries and preventing associated complications as they offer twofold benefits. However, further research is needed to determine the optimal dosage, administration route, and long-term safety of each of these Nrf2 activators in the context of respiratory viral infections in humans. Additionally, studies investigating the potential synergistic effects of combining different Nrf2 activators for enhanced therapeutic outcomes are warranted. For example, combining sulforaphane, curcumin, and resveratrol may have additive or synergistic effects in activating the Nrf2 pathway and reducing respiratory virus-induced injuries. Further research is thus needed to explore the potential benefits and safety of combining these Nrf2 activators and understand the mechanisms underlying their synergistic effects. Note, however, that most evidence supporting Nrf2 agonists for viral infection treatment comes from in vitro studies and little evidence comes from in vivo validation. These studies often overlook Nrf2 pathway regulation balance; the dysregulation of this pathway can potentially lead to cancer cell proliferation alongside overactivation. Even though in vivo experiments in mice and human trials with sulforaphane show promising outcomes, caution is needed due to potentially harmful effects from NRF2 overactivation. Thus, a further study is essential before therapeutically utilizing Nrf2 agonists alone or in combination.

10. Concluding Remarks

Respiratory virus infections are one of the main leading causes of airway damage. Respiratory virus-associated injuries include oxidative stress, ferroptosis, inflammation, pyroptosis, apoptosis, fibrosis, autoimmunity, and vascular injury. The inhibition or deregulation of the Nrf2 pathway activation induces airway tissue damage in viral respiratory infections. In contrast, Nrf2 pathway activation demonstrates protection against tissue

and organ injuries. Clinical trials of Nrf2 agonists are needed to define the effect of Nrf2 therapeutics on airway tissues and organs damaged by viral respiratory infections.

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References

1. Cilla, G.; Onate, E.; Perez-Yarza, E.G.; Montes, M.; Vicente, D.; Perez-Trallero, E. Viruses in community-acquired pneumonia in children aged less than 3 years old: High rate of viral coinfection. *J. Med. Virol.* **2008**, *80*, 1843–1849. [CrossRef] [PubMed]
2. Ruuskanen, O.; Lahti, E.; Jennings, L.C.; Murdoch, D.R. Viral pneumonia. *Lancet* **2011**, *377*, 1264–1275. [CrossRef] [PubMed]
3. Jain, S. Epidemiology of Viral Pneumonia. *Clin. Chest Med.* **2017**, *38*, 1–9. [CrossRef] [PubMed]
4. Krammer, F.; Smith, G.J.D.; Fouchier, R.A.M.; Peiris, M.; Kedzierska, K.; Doherty, P.C.; Palese, P.; Shaw, M.L.; Treanor, J.; Webster, R.G.; et al. Influenza. *Nat. Rev. Dis. Primers* **2018**, *4*, 3. [CrossRef] [PubMed]
5. Luyt, C.E.; Combes, A.; Trouillet, J.L.; Nieszkowska, A.; Chastre, J. Virus-induced acute respiratory distress syndrome: Epidemiology, management and outcome. *Presse Med.* **2011**, *40*, e561–e568. [CrossRef] [PubMed]
6. Kato, Y. Pneumonia and acute respiratory distress syndrome due to pandemic influenza H1N1 2009. *Nihon Rinsho* **2010**, *68*, 1666–1670. [PubMed]
7. Wick, K.D.; McAuley, D.F.; Levitt, J.E.; Beitler, J.R.; Annane, D.; Riviello, E.D.; Calfee, C.S.; Matthay, M.A. Promises and challenges of personalized medicine to guide ARDS therapy. *Crit. Care* **2021**, *25*, 404. [CrossRef] [PubMed]
8. Martin, T.R.; Zemans, R.L.; Ware, L.B.; Schmidt, E.P.; Riches, D.W.H.; Bastarache, L.; Calfee, C.S.; Desai, T.J.; Herold, S.; Hough, C.L.; et al. New Insights into Clinical and Mechanistic Heterogeneity of the Acute Respiratory Distress Syndrome: Summary of the Aspen Lung Conference 2021. *Am. J. Respir. Cell Mol. Biol.* **2022**, *67*, 284–308. [CrossRef] [PubMed]
9. Crowe, J.E. Human Respiratory Viruses. In *Reference Module in Biomedical Sciences*; Elsevier: Amsterdam, The Netherlands, 2014. [CrossRef]
10. Dasaraju, P.V.; Liu, C. Infections of the Respiratory System. In *Medical Microbiology*, 4th ed.; Baron, S., Ed.; Elsevier Health Sciences: Galveston, TX, USA, 1996.
11. Khomich, O.; Kochetkov, S.; Bartosch, B.; Ivanov, A. Redox Biology of Respiratory Viral Infections. *Viruses* **2018**, *10*, 392. [CrossRef]
12. Gain, C.; Song, S.; Angtuaco, T.; Satta, S.; Kelesidis, T. The role of oxidative stress in the pathogenesis of infections with coronaviruses. *Front. Microbiol.* **2023**, *13*, 1111930. [CrossRef]
13. Ivanciuc, T.; Sbrana, E.; Casola, A.; Garofalo, R.P. Protective Role of Nuclear Factor Erythroid 2-Related Factor 2 Against Respiratory Syncytial Virus and Human Metapneumovirus Infections. *Front. Immunol.* **2018**, *9*, 854. [CrossRef]
14. Biagioli, M.C.; Kaul, P.; Singh, I.; Turner, R.B. The role of oxidative stress in rhinovirus induced elaboration of IL-8 by respiratory epithelial cells. *Free Radic. Biol. Med.* **1999**, *26*, 454–462. [CrossRef]
15. Mihaylova, V.T.; Kong, Y.; Fedorova, O.; Sharma, L.; Dela Cruz, C.S.; Pyle, A.M.; Iwasaki, A.; Foxman, E.F. Regional Differences in Airway Epithelial Cells Reveal Tradeoff between Defense against Oxidative Stress and Defense against Rhinovirus. *Cell Rep.* **2018**, *24*, 3000–3007.e3003. [CrossRef]
16. Lee, S.H.; Han, M.S.; Lee, T.H.; Lee, D.B.; Park, J.H.; Lee, S.H.; Kim, T.H. Hydrogen peroxide attenuates rhinovirus-induced anti-viral interferon secretion in sinonasal epithelial cells. *Front. Immunol.* **2023**, *14*, 1086381. [CrossRef]
17. Triantafilou, K.; Kar, S.; van Kuppeveld, F.J.M.; Triantafilou, M. Rhinovirus-Induced Calcium Flux Triggers NLRP3 and NLRC5 Activation in Bronchial Cells. *Am. J. Respir. Cell Mol. Biol.* **2013**, *49*, 923–934. [CrossRef]
18. Lin, T.Y.; Hsia, S.H.; Huang, Y.C.; Wu, C.T.; Chang, L.Y. Proinflammatory Cytokine Reactions in Enterovirus 71 Infections of the Central Nervous System. *Clin. Infect. Dis.* **2003**, *36*, 269–274. [CrossRef] [PubMed]
19. Ai, F.; Zheng, J.; Zhang, Y.; Fan, T. Inhibition of 12/15-LO ameliorates CVB3-induced myocarditis by activating Nrf2. *Chem.-Biol. Interact.* **2017**, *272*, 65–71. [CrossRef]
20. Santangelo, R.; Mancuso, C.; Marchetti, S.; Di Stasio, E.; Pani, G.; Fadda, G. Bilirubin: An Endogenous Molecule with Antiviral Activity In Vitro. *Front. Pharmacol.* **2012**, *3*, 36. [CrossRef] [PubMed]
21. Huang, C.; Feng, F.; Shi, Y.; Li, W.; Wang, Z.; Zhu, Y.; Yuan, S.; Hu, D.; Dai, J.; Jiang, Q.; et al. Protein Kinase C Inhibitors Reduce SARS-CoV-2 Replication in Cultured Cells. *Microbiol. Spectr.* **2022**, *10*, e0105622. [CrossRef] [PubMed]
22. Cuadrado, A.; Pajares, M.; Benito, C.; Jimenez-Villegas, J.; Escoll, M.; Fernandez-Gines, R.; Garcia Yague, A.J.; Lastra, D.; Manda, G.; Rojo, A.I.; et al. Can Activation of NRF2 Be a Strategy against COVID-19? *Trends Pharmacol. Sci.* **2020**, *41*, 598–610. [CrossRef]
23. Zhao, S.; Ghosh, A.; Lo, C.S.; Chenier, I.; Scholey, J.W.; Filep, J.G.; Ingelfinger, J.R.; Zhang, S.L.; Chan, J.S.D. Nrf2 Deficiency Upregulates Intrarenal Angiotensin-Converting Enzyme-2 and Angiotensin 1–7 Receptor Expression and Attenuates Hypertension and Nephropathy in Diabetic Mice. *Endocrinology* **2018**, *159*, 836–852. [CrossRef]

24. Gao, Y.; Yan, L.; Huang, Y.; Liu, F.; Zhao, Y.; Cao, L.; Wang, T.; Sun, Q.; Ming, Z.; Zhang, L.; et al. Structure of the RNA-dependent RNA polymerase from COVID-19 virus. *Science* **2020**, *368*, 779–782. [CrossRef]
25. Olagnier, D.; Farahani, E.; Thyrsted, J.; Blay-Cadanet, J.; Herengt, A.; Idorn, M.; Hait, A.; Hernaez, B.; Knudsen, A.; Iversen, M.B.; et al. SARS-CoV2-mediated suppression of NRF2-signaling reveals potent antiviral and anti-inflammatory activity of 4-octyl-itaconate and dimethyl fumarate. *Nat. Commun.* **2020**, *11*, 4938. [CrossRef]
26. Qu, Y.; Haas de Mello, A.; Morris, D.R.; Jones-Hall, Y.L.; Ivanciuc, T.; Sattler, R.A.; Paessler, S.; Menachery, V.D.; Garofalo, R.P.; Casola, A. SARS-CoV-2 Inhibits NRF2-Mediated Antioxidant Responses in Airway Epithelial Cells and in the Lung of a Murine Model of Infection. *Microbiol. Spectr.* **2023**, *11*, e0037823. [CrossRef]
27. Batra, N.; De Souza, C.; Batra, J.; Raetz, A.G.; Yu, A.M. The HMOX1 Pathway as a Promising Target for the Treatment and Prevention of SARS-CoV-2 of 2019 (COVID-19). *Int. J. Mol. Sci.* **2020**, *21*, 641. [CrossRef]
28. Luo, X.H.; Zhu, Y.; Mao, J.; Du, R.C. T cell immunobiology and cytokine storm of COVID-19. *Scand. J. Immunol.* **2021**, *93*, e12989. [CrossRef]
29. Hua, C.C.; Chang, L.C.; Tseng, J.C.; Chu, C.M.; Liu, Y.C.; Shieh, W.B. Functional haplotypes in the promoter region of transcription factor Nrf2 in chronic obstructive pulmonary disease. *Dis. Markers* **2010**, *28*, 185–193. [CrossRef]
30. Hosakote, Y.M.; Liu, T.; Castro, S.M.; Garofalo, R.P.; Casola, A. Respiratory syncytial virus induces oxidative stress by modulating antioxidant enzymes. *Am. J. Respir. Cell Mol. Biol.* **2009**, *41*, 348–357. [CrossRef]
31. Casola, A.; Burger, N.; Liu, T.; Jamaluddin, M.; Brasier, A.R.; Garofalo, R.P. Oxidant tone regulates RANTES gene expression in airway epithelial cells infected with respiratory syncytial virus. Role in viral-induced interferon regulatory factor activation. *J. Biol. Chem.* **2001**, *276*, 19715–19722. [CrossRef]
32. Liu, T.; Castro, S.; Brasier, A.R.; Jamaluddin, M.; Garofalo, R.P.; Casola, A. Reactive oxygen species mediate virus-induced STAT activation: Role of tyrosine phosphatases. *J. Biol. Chem.* **2004**, *279*, 2461–2469. [CrossRef]
33. Komaravelli, N.; Ansar, M.; Garofalo, R.P.; Casola, A. Respiratory syncytial virus induces NRF2 degradation through a promyelocytic leukemia protein–ring finger protein 4 dependent pathway. *Free Radic. Biol. Med.* **2017**, *113*, 494–504. [CrossRef] [PubMed]
34. Ren, K.; Lv, Y.; Zhuo, Y.; Chen, C.; Shi, H.; Guo, L.; Yang, G.; Hou, Y.; Tan, R.X.; Li, E. Suppression of IRG-1 Reduces Inflammatory Cell Infiltration and Lung Injury in Respiratory Syncytial Virus Infection by Reducing Production of Reactive Oxygen Species. *J. Virol.* **2016**, *90*, 7313–7322. [CrossRef] [PubMed]
35. Mills, E.L.; Ryan, D.G.; Prag, H.A.; Dikovskaya, D.; Menon, D.; Zaslona, Z.; Jedrychowski, M.P.; Costa, A.S.H.; Higgins, M.; Hams, E.; et al. Itaconate is an anti-inflammatory metabolite that activates Nrf2 via alkylation of KEAP1. *Nature* **2018**, *556*, 113–117. [CrossRef]
36. San-Juan-Vergara, H.; Peeples, M.E.; Lockey, R.F.; Mohapatra, S.S. Protein kinase C-alpha activity is required for respiratory syncytial virus fusion to human bronchial epithelial cells. *J. Virol.* **2004**, *78*, 13717–13726. [CrossRef] [PubMed]
37. Castro, S.M.; Guerrero-Plata, A.; Suarez-Real, G.; Adegboyega, P.A.; Colasurdo, G.N.; Khan, A.M.; Garofalo, R.P.; Casola, A. Antioxidant treatment ameliorates respiratory syncytial virus-induced disease and lung inflammation. *Am. J. Respir. Crit. Care Med.* **2006**, *174*, 1361–1369. [CrossRef] [PubMed]
38. Espinoza, J.A.; Leon, M.A.; Cespedes, P.F.; Gomez, R.S.; Canedo-Marroquin, G.; Riquelme, S.A.; Salazar-Echegarai, F.J.; Blancou, P.; Simon, T.; Anegon, I.; et al. Heme Oxygenase-1 Modulates Human Respiratory Syncytial Virus Replication and Lung Pathogenesis during Infection. *J. Immunol.* **2017**, *199*, 212–223. [CrossRef]
39. Cho, H.Y.; Imani, F.; Miller-DeGraff, L.; Walters, D.; Melendi, G.A.; Yamamoto, M.; Polack, F.P.; Kleeberger, S.R. Antiviral activity of Nrf2 in a murine model of respiratory syncytial virus disease. *Am. J. Respir. Crit. Care Med.* **2009**, *179*, 138–150. [CrossRef] [PubMed]
40. Segovia, J.; Sabbah, A.; Mgbemena, V.; Tsai, S.Y.; Chang, T.H.; Berton, M.T.; Morris, I.R.; Allen, I.C.; Ting, J.P.; Bose, S. TLR2/MyD88/NF-kappaB pathway, reactive oxygen species, potassium efflux activates NLRP3/ASC inflammasome during respiratory syncytial virus infection. *PLoS ONE* **2012**, *7*, e29695. [CrossRef] [PubMed]
41. Triantafilou, K.; Kar, S.; Vakakis, E.; Kotecha, S.; Triantafilou, M. Human respiratory syncytial virus viroporin SH: A viral recognition pathway used by the host to signal inflammasome activation. *Thorax* **2013**, *68*, 66–75. [CrossRef]
42. Reed, J.L.; Brewah, Y.A.; Delaney, T.; Welliver, T.; Burwell, T.; Benjamin, E.; Kuta, E.; Kozhich, A.; McKinney, L.; Suzich, J.; et al. Macrophage impairment underlies airway occlusion in primary respiratory syncytial virus bronchiolitis. *J. Infect. Dis.* **2008**, *198*, 1783–1793. [CrossRef]
43. Mondal, A.; Dawson, A.R.; Potts, G.K.; Freiberger, E.C.; Baker, S.F.; Moser, L.A.; Bernard, K.A.; Coon, J.J.; Mehle, A. Influenza virus recruits host protein kinase C to control assembly and activity of its replication machinery. *Elife* **2017**, *6*, e26910. [CrossRef] [PubMed]
44. Kesic, M.J.; Simmons, S.O.; Bauer, R.; Jaspers, I. Nrf2 expression modifies influenza A entry and replication in nasal epithelial cells. *Free Radic. Biol. Med.* **2011**, *51*, 444–453. [CrossRef]
45. Kosmider, B.; Messier, E.M.; Janssen, W.J.; Nahreini, P.; Wang, J.; Hartshorn, K.L.; Mason, R.J. Nrf2 protects human alveolar epithelial cells against injury induced by influenza A virus. *Respir. Res.* **2012**, *13*, 43. [CrossRef] [PubMed]
46. Shoji, M.; Arakaki, Y.; Esumi, T.; Kohnomi, S.; Yamamoto, C.; Suzuki, Y.; Takahashi, E.; Konishi, S.; Kido, H.; Kuzuhara, T. Bakuchiol Is a Phenolic Isoprenoid with Novel Enantiomer-selective Anti-influenza A Virus Activity Involving Nrf2 Activation. *J. Biol. Chem.* **2015**, *290*, 28001–28017. [CrossRef] [PubMed]

47. Ma, L.L.; Wang, H.Q.; Wu, P.; Hu, J.; Yin, J.Q.; Wu, S.; Ge, M.; Sun, W.F.; Zhao, J.Y.; Aisa, H.A.; et al. Rupestonic acid derivative YZH-106 suppresses influenza virus replication by activation of heme oxygenase-1-mediated interferon response. *Free Radic. Biol. Med.* **2016**, *96*, 347–361. [CrossRef] [PubMed]
48. Yageta, Y.; Ishii, Y.; Morishima, Y.; Masuko, H.; Ano, S.; Yamadori, T.; Itoh, K.; Takeuchi, K.; Yamamoto, M.; Hizawa, N. Role of Nrf2 in host defense against influenza virus in cigarette smoke-exposed mice. *J. Virol.* **2011**, *85*, 4679–4690. [CrossRef] [PubMed]
49. McAuley, J.L.; Tate, M.D.; MacKenzie-Kludas, C.J.; Pinar, A.; Zeng, W.; Stutz, A.; Latz, E.; Brown, L.E.; Mansell, A. Activation of the NLRP3 inflammasome by IAV virulence protein PB1-F2 contributes to severe pathophysiology and disease. *PLoS Pathog.* **2013**, *9*, e1003392. [CrossRef] [PubMed]
50. Schneider, C.; Nobs, S.P.; Heer, A.K.; Kurrer, M.; Klinke, G.; van Rooijen, N.; Vogel, J.; Kopf, M. Alveolar macrophages are essential for protection from respiratory failure and associated morbidity following influenza virus infection. *PLoS Pathog.* **2014**, *10*, e1004053. [CrossRef] [PubMed]
51. Zhang, C.; Zhang, K.; Zang, G.; Chen, T.; Lu, N.; Wang, S.; Zhang, G. Curcumin Inhibits Replication of Human Parainfluenza Virus Type 3 by Affecting Viral Inclusion Body Formation. *Biomed. Res. Int.* **2021**, *2021*, 1807293. [CrossRef]
52. Ashrafizadeh, M.; Ahmadi, Z.; Mohammadinejad, R.; Farkhondeh, T.; Samarghandian, S. Curcumin Activates the Nrf2 Pathway and Induces Cellular Protection Against Oxidative Injury. *Curr. Mol. Med.* **2020**, *20*, 116–133. [CrossRef]
53. Moreno-Solís, G.; dela Torre-Aguilar, M.J.; Torres-Borrego, J.; Llorente-Cantarero, F.J.; Fernández-Gutiérrez, F.; Gil-Campos, M.; Túnez-Fiñana, I.; Pérez-Navero, J.L. Oxidative stress and inflamatory plasma biomarkers in respiratory syncytial virus bronchiolitis. *Clin. Respir. J.* **2016**, *11*, 839–846. [CrossRef]
54. Garcia-Sanchez, A.; Miranda-Diaz, A.G.; Cardona-Munoz, E.G. The Role of Oxidative Stress in Physiopathology and Pharmacological Treatment with Pro- and Antioxidant Properties in Chronic Diseases. *Oxid. Med. Cell. Longev.* **2020**, *2020*, 2082145. [CrossRef]
55. Moi, P.; Chan, K.; Asunis, I.; Cao, A.; Kan, Y.W. Isolation of NF-E2-related factor 2 (Nrf2), a NF-E2-like basic leucine zipper transcriptional activator that binds to the tandem NF-E2/AP1 repeat of the beta-globin locus control region. *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 9926–9930. [CrossRef]
56. Polyak, S.J.; Yu, J.-S.; Chen, W.-C.; Tseng, C.-K.; Lin, C.-K.; Hsu, Y.-C.; Chen, Y.-H.; Lee, J.-C. Sulforaphane Suppresses Hepatitis C Virus Replication by Up-Regulating Heme Oxygenase-1 Expression through PI3K/Nrf2 Pathway. *PLoS ONE* **2016**, *11*, e0152236. [CrossRef]
57. Tseng, C.-K.; Hsu, S.-P.; Lin, C.-K.; Wu, Y.-H.; Lee, J.-C.; Young, K.-C. Celastrol inhibits hepatitis C virus replication by upregulating heme oxygenase-1 via the JNK MAPK/Nrf2 pathway in human hepatoma cells. *Antivir. Res.* **2017**, *146*, 191–200. [CrossRef]
58. Chen, M.-H.; Lee, M.-Y.; Chuang, J.-J.; Li, Y.-Z.; Ning, S.-T.; Chen, J.-C.; Liu, Y.-W. Curcumin inhibits HCV replication by induction of heme oxygenase-1 and suppression of AKT. *Int. J. Mol. Med.* **2012**, *30*, 1021–1028. [CrossRef]
59. Ashida, H.; Mimuro, H.; Ogawa, M.; Kobayashi, T.; Sanada, T.; Kim, M.; Sasakawa, C. Cell death and infection: A double-edged sword for host and pathogen survival. *J. Cell Biol.* **2011**, *195*, 931–942. [CrossRef]
60. Fink, S.L.; Cookson, B.T. Apoptosis, pyroptosis, and necrosis: Mechanistic description of dead and dying eukaryotic cells. *Infect. Immun.* **2005**, *73*, 1907–1916. [CrossRef]
61. Lamkanfi, M.; Dixit, V.M. Manipulation of host cell death pathways during microbial infections. *Cell Host Microbe* **2010**, *8*, 44–54. [CrossRef]
62. Morais da Silva, M.; Lira de Lucena, A.S.; Paiva Junior, S.S.L.; Florencio De Carvalho, V.M.; Santana de Oliveira, P.S.; da Rosa, M.M.; Barreto de Melo Rego, M.J.; Pitta, M.; Pereira, M.C. Cell death mechanisms involved in cell injury caused by SARS-CoV-2. *Rev. Med. Virol.* **2022**, *32*, e2292. [CrossRef]
63. Chakkittukandiyil, A.; Sajini, D.V.; Karuppaiah, A.; Selvaraj, D. The principal molecular mechanisms behind the activation of Keap1/Nrf2/ARE pathway leading to neuroprotective action in Parkinson's disease. *Neurochem. Int.* **2022**, *156*, 105325. [CrossRef]
64. Ishii, T.; Warabi, E.; Mann, G.E. Mechanisms underlying Nrf2 nuclear translocation by non-lethal levels of hydrogen peroxide: p38 MAPK-dependent neutral sphingomyelinase2 membrane trafficking and ceramide/PKCzeta/CK2 signaling. *Free Radic. Biol. Med.* **2022**, *191*, 191–202. [CrossRef]
65. Folkerts, G.; Kloek, J.; Muijsers, R.B.; Nijkamp, F.P. Reactive nitrogen and oxygen species in airway inflammation. *Eur. J. Pharmacol.* **2001**, *429*, 251–262. [CrossRef]
66. Castro, R.; Pinzon, H.S.; Alvis-Guzman, N. A systematic review of observational studies on oxidative/nitrosative stress involvement in dengue pathogenesis. *Colomb. Med.* **2015**, *46*, 135–143. [CrossRef]
67. Shields, H.J.; Traa, A.; Van Raamsdonk, J.M. Beneficial and Detrimental Effects of Reactive Oxygen Species on Lifespan: A Comprehensive Review of Comparative and Experimental Studies. *Front. Cell Dev. Biol.* **2021**, *9*, 628157. [CrossRef] [PubMed]
68. Zgorzynska, E.; Dziedzic, B.; Walczewska, A. An Overview of the Nrf2/ARE Pathway and Its Role in Neurodegenerative Diseases. *Int. J. Mol. Sci.* **2021**, *22*, 9592. [CrossRef] [PubMed]
69. He, F.; Ru, X.; Wen, T. NRF2, a Transcription Factor for Stress Response and Beyond. *Int. J. Mol. Sci.* **2020**, *21*, 4777. [CrossRef]
70. McCord, J.M.; Gao, B.; Hybertson, B.M. The Complex Genetic and Epigenetic Regulation of the Nrf2 Pathways: A Review. *Antioxidants* **2023**, *12*, 366. [CrossRef]
71. Dixon, S.J.; Lemberg, K.M.; Lamprecht, M.R.; Skouta, R.; Zaitsev, E.M.; Gleason, C.E.; Patel, D.N.; Bauer, A.J.; Cantley, A.M.; Yang, W.S.; et al. Ferroptosis: An Iron-Dependent Form of Nonapoptotic Cell Death. *Cell* **2012**, *149*, 1060–1072. [CrossRef]

72. Lin, Z.; Yang, X.; Guan, L.; Qin, L.; Ding, J.; Zhou, L. The link between ferroptosis and airway inflammatory diseases: A novel target for treatment. *Front. Mol. Biosci.* **2022**, *9*, 985571. [CrossRef]
73. Roulston, A.; Marcellus, R.C.; Branton, P.E. Viruses and apoptosis. *Annu. Rev. Microbiol.* **1999**, *53*, 577–628. [CrossRef]
74. Everett, H.; McFadden, G. Apoptosis: An innate immune response to virus infection. *Trends Microbiol.* **1999**, *7*, 160–165. [CrossRef] [PubMed]
75. Nencioni, L.; Iuvara, A.; Aquilano, K.; Ciriolo, M.R.; Cozzolino, F.; Rotilio, G.; Garaci, E.; Palamara, A.T. Influenza A virus replication is dependent on an antioxidant pathway that involves GSH and Bcl-2. *FASEB J.* **2003**, *17*, 758–760. [CrossRef] [PubMed]
76. Alsuwaidi, A.R.; Almarzooqi, S.; Albawardi, A.; Benedict, S.; Kochiyil, J.; Mustafa, F.; Hartwig, S.M.; Varga, S.M.; Souid, A.-K. Cellular bioenergetics, caspase activity and glutathione in murine lungs infected with influenza A virus. *Virology* **2013**, *446*, 180–188. [CrossRef] [PubMed]
77. Kumar, R.; Nayak, M.; Sahoo, G.C.; Pandey, K.; Sarkar, M.C.; Ansari, Y.; Das, V.N.R.; Topno, R.K.; Bhawna; Madhukar, M.; et al. Iron oxide nanoparticles based antiviral activity of H1N1 influenza A virus. *J. Infect. Chemother.* **2019**, *25*, 325–329. [CrossRef] [PubMed]
78. Zhao, X.; Zhang, Y.; Luo, B. Ferroptosis, from the virus point of view: Opportunities and challenges. *Crit. Rev. Microbiol.* **2024**, 1–18. [CrossRef] [PubMed]
79. Edeas, M.; Saleh, J.; Peyssonnaux, C. Iron: Innocent bystander or vicious culprit in COVID-19 pathogenesis? *Int. J. Infect. Dis.* **2020**, *97*, 303–305. [CrossRef] [PubMed]
80. Cavezzi, A.; Troiani, E.; Corrao, S. COVID-19: Hemoglobin, Iron, and Hypoxia beyond Inflammation. A Narrative Review. *Clin. Pract.* **2020**, *10*, 1271. [CrossRef] [PubMed]
81. Jacobs, W.; Lammens, M.; Kerckhofs, A.; Voets, E.; Van San, E.; Van Coillie, S.; Peleman, C.; Mergeay, M.; Sirimsi, S.; Matheeussen, V.; et al. Fatal lymphocytic cardiac damage in coronavirus disease 2019 (COVID-19): Autopsy reveals a ferroptosis signature. *ESC Heart Fail.* **2020**, *7*, 3772–3781. [CrossRef] [PubMed]
82. Imai, Y.; Kuba, K.; Neely, G.G.; Yaghubian-Malhami, R.; Perkmann, T.; van Loo, G.; Ermolaeva, M.; Veldhuizen, R.; Leung, Y.H.C.; Wang, H.; et al. Identification of Oxidative Stress and Toll-like Receptor 4 Signaling as a Key Pathway of Acute Lung Injury. *Cell* **2008**, *133*, 235–249. [CrossRef]
83. Wang, B.; Shen, W.B.; Yang, P.; Turan, S. SARS-CoV-2 infection induces activation of ferroptosis in human placenta. *Front. Cell Dev. Biol.* **2022**, *10*, 1022747. [CrossRef] [PubMed]
84. Kinowaki, Y.; Kurata, M.; Ishibashi, S.; Ikeda, M.; Tatsuzawa, A.; Yamamoto, M.; Miura, O.; Kitagawa, M.; Yamamoto, K. Glutathione peroxidase 4 overexpression inhibits ROS-induced cell death in diffuse large B-cell lymphoma. *Lab. Investig.* **2018**, *98*, 609–619. [CrossRef] [PubMed]
85. Jain, S.K.; Kahlon, G.; Bass, P.; Levine, S.N.; Warden, C. Can L-Cysteine and Vitamin D Rescue Vitamin D and Vitamin D Binding Protein Levels in Blood Plasma of African American Type 2 Diabetic Patients? *Antioxid. Redox Signal* **2015**, *23*, 688–693. [CrossRef]
86. Forman, H.J.; Zhang, H.; Rinna, A. Glutathione: Overview of its protective roles, measurement, and biosynthesis. *Mol. Asp. Med.* **2009**, *30*, 1–12. [CrossRef]
87. Parsanathan, R.; Jain, S.K. Glutathione deficiency induces epigenetic alterations of vitamin D metabolism genes in the livers of high-fat diet-fed obese mice. *Sci. Rep.* **2019**, *9*, 14784. [CrossRef] [PubMed]
88. Polonikov, A. Endogenous Deficiency of Glutathione as the Most Likely Cause of Serious Manifestations and Death in COVID-19 Patients. *ACS Infect. Dis.* **2020**, *6*, 1558–1562. [CrossRef]
89. Zhou, F.; Yu, T.; Du, R.; Fan, G.; Liu, Y.; Liu, Z.; Xiang, J.; Wang, Y.; Song, B.; Gu, X.; et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. *Lancet* **2020**, *395*, 1054–1062. [CrossRef]
90. Salimi, V.; Ramezani, A.; Mirzaei, H.; Tahamtan, A.; Faghihloo, E.; Rezaei, F.; Naseri, M.; Bont, L.; Mokhtari-Azad, T.; Tavakoli-Yaraki, M. Evaluation of the expression level of 12/15 lipoxygenase and the related inflammatory factors (CCL5, CCL3) in respiratory syncytial virus infection in mice model. *Microb. Pathog.* **2017**, *109*, 209–213. [CrossRef]
91. Wang, H.; Li, Z.; Niu, J.; Xu, Y.; Ma, L.; Lu, A.; Wang, X.; Qian, Z.; Huang, Z.; Jin, X.; et al. Antiviral effects of ferric ammonium citrate. *Cell Discov.* **2018**, *4*, 14. [CrossRef]
92. Lin, T.Y.; Chu, C.; Chiu, C.H. Lactoferrin Inhibits Enterovirus 71 Infection of Human Embryonal Rhabdomyosarcoma Cells In Vitro. *J. Infect. Dis.* **2002**, *186*, 1161–1164. [CrossRef]
93. Wu, K.C.; Cui, J.Y.; Klaassen, C.D. Beneficial role of Nrf2 in regulating NADPH generation and consumption. *Toxicol. Sci.* **2011**, *123*, 590–600. [CrossRef] [PubMed]
94. Lee, J.M.; Calkins, M.J.; Chan, K.; Kan, Y.W.; Johnson, J.A. Identification of the NF-E2-related factor-2-dependent genes conferring protection against oxidative stress in primary cortical astrocytes using oligonucleotide microarray analysis. *J. Biol. Chem.* **2003**, *278*, 12029–12038. [CrossRef] [PubMed]
95. Sasaki, H.; Sato, H.; Kuriyama-Matsumura, K.; Sato, K.; Maebara, K.; Wang, H.; Tamba, M.; Itoh, K.; Yamamoto, M.; Bannai, S. Electrophile response element-mediated induction of the cystine/glutamate exchange transporter gene expression. *J. Biol. Chem.* **2002**, *277*, 44765–44771. [CrossRef]
96. Liu, C.; Wu, X.; Bing, X.; Qi, W.; Zhu, F.; Guo, N.; Li, C.; Gao, X.; Cao, X.; Zhao, M.; et al. H1N1 influenza virus infection through NRF2-KEAP1-GCLC pathway induces ferroptosis in nasal mucosal epithelial cells. *Free Radic. Biol. Med.* **2023**, *204*, 226–242. [CrossRef]

97. Wei, Y.; Gu, Y.; Zhou, Z.; Wu, C.; Liu, Y.; Sun, H. TRIM21 Promotes Oxidative Stress and Ferroptosis through the SQSTM1-NRF2-KEAP1 Axis to Increase the Titers of H5N1 Highly Pathogenic Avian Influenza Virus. *Int. J. Mol. Sci.* **2024**, *25*, 3315. [CrossRef] [PubMed]
98. Zhou, B.; Wang, L.; Yang, S.; Liang, Y.; Zhang, Y.; Liu, X.; Pan, X.; Li, J. Pyrogallol protects against influenza A virus-triggered lethal lung injury by activating the Nrf2-PPAR-gamma-HO-1 signaling axis. *MedComm* **2024**, *5*, e531. [CrossRef] [PubMed]
99. Nguyen, V.; Zhang, Y.; Gao, C.; Cao, X.; Tian, Y.; Carver, W.; Kiaris, H.; Cui, T.; Tan, W. The Spike Protein of SARS-CoV-2 Impairs Lipid Metabolism and Increases Susceptibility to Lipotoxicity: Implication for a Role of Nrf2. *Cells* **2022**, *11*, 1916. [CrossRef] [PubMed]
100. Naidu, S.A.G.; Clemens, R.A.; Naidu, A.S. SARS-CoV-2 Infection Dysregulates Host Iron (Fe)-Redox Homeostasis (Fe-R-H): Role of Fe-Redox Regulators, Ferroptosis Inhibitors, Anticoagulants, and Iron-Chelators in COVID-19 Control. *J. Diet. Suppl.* **2023**, *20*, 312–371. [CrossRef] [PubMed]
101. Liu, L.; Du, J.; Yang, S.; Zheng, B.; Shen, J.; Huang, J.; Cao, L.; Huang, S.; Liu, X.; Guo, L.; et al. SARS-CoV-2 ORF3a sensitizes cells to ferroptosis via Keap1-NRF2 axis. *Redox Biol.* **2023**, *63*, 102752. [CrossRef] [PubMed]
102. Yan, R.; Lin, B.; Jin, W.; Tang, L.; Hu, S.; Cai, R. NRF2, a Superstar of Ferroptosis. *Antioxidants* **2023**, *12*, 1739. [CrossRef]
103. Vareille, M.; Kieninger, E.; Edwards, M.R.; Regamey, N. The airway epithelium: Soldier in the fight against respiratory viruses. *Clin. Microbiol. Rev.* **2011**, *24*, 210–229. [CrossRef] [PubMed]
104. Braciale, T.J.; Sun, J.; Kim, T.S. Regulating the adaptive immune response to respiratory virus infection. *Nat. Rev. Immunol.* **2012**, *12*, 295–305. [CrossRef] [PubMed]
105. Tan, K.S.; Lim, R.L.; Liu, J.; Ong, H.H.; Tan, V.J.; Lim, H.F.; Chung, K.F.; Adcock, I.M.; Chow, V.T.; Wang, Y. Respiratory Viral Infections in Exacerbation of Chronic Airway Inflammatory Diseases: Novel Mechanisms and Insights From the Upper Airway Epithelium. *Front. Cell Dev. Biol.* **2020**, *8*, 99. [CrossRef] [PubMed]
106. Cheung, C.Y.; Poon, L.L.; Lau, A.S.; Luk, W.; Lau, Y.L.; Shortridge, K.F.; Gordon, S.; Guan, Y.; Peiris, J.S. Induction of proinflammatory cytokines in human macrophages by influenza A (H5N1) viruses: A mechanism for the unusual severity of human disease? *Lancet* **2002**, *360*, 1831–1837. [CrossRef] [PubMed]
107. Costa, L.D.; Costa, P.S.; Camargos, P.A. Exacerbation of asthma and airway infection: Is the virus the villain? *J. Pediatr.* **2014**, *90*, 542–555. [CrossRef] [PubMed]
108. Short, K.R.; Kasper, J.; van der Aa, S.; Andeweg, A.C.; Zaaraoui-Boutahar, F.; Goeijenbier, M.; Richard, M.; Herold, S.; Becker, C.; Scott, D.P.; et al. Influenza virus damages the alveolar barrier by disrupting epithelial cell tight junctions. *Eur. Respir. Soc.* **2016**, *47*, 954–966. [CrossRef] [PubMed]
109. Gu, Y.; Zuo, X.; Zhang, S.; Ouyang, Z.; Jiang, S.; Wang, F.; Wang, G. The Mechanism behind Influenza Virus Cytokine Storm. *Viruses* **2021**, *13*, 1362. [CrossRef] [PubMed]
110. Monteleone, M.; Stanley, A.C.; Chen, K.W.; Brown, D.L.; Bezbradica, J.S.; von Pein, J.B.; Holley, C.L.; Boucher, D.; Shakespear, M.R.; Kapetanovic, R.; et al. Interleukin-1beta Maturation Triggers Its Relocation to the Plasma Membrane for Gasdermin-D-Dependent and -Independent Secretion. *Cell Rep.* **2018**, *24*, 1425–1433. [CrossRef] [PubMed]
111. Carty, M.; Kearney, J.; Shanahan, K.A.; Hams, E.; Sugisawa, R.; Connolly, D.; Doran, C.G.; Munoz-Wolf, N.; Gurtler, C.; Fitzgerald, K.A.; et al. Cell Survival and Cytokine Release after Inflammasome Activation Is Regulated by the Toll-IL-1R Protein SARM. *Immunity* **2019**, *50*, 1412–1424.e1416. [CrossRef] [PubMed]
112. Xia, S.; Hollingsworth, L.R.; Wu, H. Mechanism and Regulation of Gasdermin-Mediated Cell Death. *Cold Spring Harb. Perspect. Biol.* **2020**, *12*, a036400. [CrossRef]
113. Zhang, Y.; Dong, Z.; Song, W. NLRP3 inflammasome as a novel therapeutic target for Alzheimer's disease. *Signal Transduct. Target. Ther.* **2020**, *5*, 37. [CrossRef] [PubMed]
114. Broz, P.; Dixit, V.M. Inflammasomes: Mechanism of assembly, regulation and signalling. *Nat. Rev. Immunol.* **2016**, *16*, 407–420. [CrossRef] [PubMed]
115. Swanson, K.V.; Deng, M.; Ting, J.P. The NLRP3 inflammasome: Molecular activation and regulation to therapeutics. *Nat. Rev. Immunol.* **2019**, *19*, 477–489. [CrossRef] [PubMed]
116. Kelley, N.; Jeltema, D.; Duan, Y.; He, Y. The NLRP3 Inflammasome: An Overview of Mechanisms of Activation and Regulation. *Int. J. Mol. Sci.* **2019**, *20*, 3328. [CrossRef] [PubMed]
117. Sims, J.E.; Smith, D.E. The IL-1 family: Regulators of immunity. *Nat. Rev. Immunol.* **2010**, *10*, 89–102. [CrossRef] [PubMed]
118. Dinarello, C.A. Immunological and inflammatory functions of the interleukin-1 family. *Annu. Rev. Immunol.* **2009**, *27*, 519–550. [CrossRef] [PubMed]
119. Shen, Y.; Qian, L.; Luo, H.; Li, X.; Ruan, Y.; Fan, R.; Si, Z.; Chen, Y.; Li, L.; Liu, Y. The Significance of NLRP Inflammasome in Neuropsychiatric Disorders. *Brain Sci.* **2022**, *12*, 1057. [CrossRef] [PubMed]
120. Bader, S.M.; Cooney, J.P.; Pellegrini, M.; Doerflinger, M. Programmed cell death: The pathways to severe COVID-19? *Biochem. J.* **2022**, *479*, 609–628. [CrossRef] [PubMed]
121. Karki, R.; Kanneganti, T.D. Innate immunity, cytokine storm, and inflammatory cell death in COVID-19. *J. Transl. Med.* **2022**, *20*, 542. [CrossRef] [PubMed]
122. Cerato, J.A.; da Silva, E.F.; Porto, B.N. Breaking Bad: Inflammasome Activation by Respiratory Viruses. *Biology* **2023**, *12*, 943. [CrossRef]

123. van den Berg, D.F.; Te Velde, A.A. Severe COVID-19: NLRP3 Inflammasome Dysregulated. *Front. Immunol.* **2020**, *11*, 1580. [CrossRef]
124. Chan, M.C.; Cheung, C.Y.; Chui, W.H.; Tsao, S.W.; Nicholls, J.M.; Chan, Y.O.; Chan, R.W.; Long, H.T.; Poon, L.L.; Guan, Y.; et al. Proinflammatory cytokine responses induced by influenza A (H5N1) viruses in primary human alveolar and bronchial epithelial cells. *Respir. Res.* **2005**, *6*, 135. [CrossRef] [PubMed]
125. Sanders, C.J.; Doherty, P.C.; Thomas, P.G. Respiratory epithelial cells in innate immunity to influenza virus infection. *Cell Tissue Res.* **2011**, *343*, 13–21. [CrossRef]
126. Bauer, L.; Rijsbergen, L.C.; Leijten, L.; Benavides, F.F.; Noack, D.; Lamers, M.M.; Haagmans, B.L.; de Vries, R.D.; de Swart, R.L.; van Riel, D. The pro-inflammatory response to influenza A virus infection is fueled by endothelial cells. *Life Sci. Alliance* **2023**, *6*. [CrossRef]
127. Zhang, S.; Wang, J.; Wang, L.; Aliyari, S.; Cheng, G. SARS-CoV-2 virus NSP14 Impairs NRF2/HMOX1 activation by targeting Sirtuin 1. *Cell. Mol. Immunol.* **2022**, *19*, 872–882. [CrossRef]
128. Lee, S.; Channappanavar, R.; Kanneganti, T.-D. Coronaviruses: Innate Immunity, Inflammasome Activation, Inflammatory Cell Death, and Cytokines. *Trends Immunol.* **2020**, *41*, 1083–1099. [CrossRef]
129. Fruhbeck, G.; Catalan, V.; Valenti, V.; Moncada, R.; Gomez-Ambrosi, J.; Becerril, S.; Silva, C.; Portincasa, P.; Escalada, J.; Rodriguez, A. FNDC4 and FNDC5 reduce SARS-CoV-2 entry points and spike glycoprotein S1-induced pyroptosis, apoptosis, and necroptosis in human adipocytes. *Cell. Mol. Immunol.* **2021**, *18*, 2457–2459. [CrossRef]
130. Li, S.; Jiang, L.; Li, X.; Lin, F.; Wang, Y.; Li, B.; Jiang, T.; An, W.; Liu, S.; Liu, H.; et al. Clinical and pathological investigation of patients with severe COVID-19. *JCI Insight* **2020**, *5*, e138070. [CrossRef] [PubMed]
131. Kobayashi, E.H.; Suzuki, T.; Funayama, R.; Nagashima, T.; Hayashi, M.; Sekine, H.; Tanaka, N.; Moriguchi, T.; Motohashi, H.; Nakayama, K.; et al. Nrf2 suppresses macrophage inflammatory response by blocking proinflammatory cytokine transcription. *Nat. Commun.* **2016**, *7*, 11624. [CrossRef] [PubMed]
132. Saha, S.; Buttari, B.; Panieri, E.; Profumo, E.; Saso, L. An Overview of Nrf2 Signaling Pathway and Its Role in Inflammation. *Molecules* **2020**, *25*, 5474. [CrossRef]
133. Rojo, A.I.; Innamorato, N.G.; Martin-Moreno, A.M.; De Ceballos, M.L.; Yamamoto, M.; Cuadrado, A. Nrf2 regulates microglial dynamics and neuroinflammation in experimental Parkinson's disease. *Glia* **2010**, *58*, 588–598. [CrossRef] [PubMed]
134. Cummins, N.W.; Weaver, E.A.; May, S.M.; Croatt, A.J.; Foreman, O.; Kennedy, R.B.; Poland, G.A.; Barry, M.A.; Nath, K.A.; Badley, A.D. Heme oxygenase-1 regulates the immune response to influenza virus infection and vaccination in aged mice. *FASEB J.* **2012**, *26*, 2911–2918. [CrossRef]
135. Wang, C.; Zhang, Y.; Han, L.; Guo, L.; Zhong, H.; Wang, J. Hemin ameliorates influenza pneumonia by attenuating lung injury and regulating the immune response. *Int. J. Antimicrob. Agents* **2017**, *49*, 45–52. [CrossRef] [PubMed]
136. Xu, Z.; Kombe Kombe, A.J.; Deng, S.; Zhang, H.; Wu, S.; Ruan, J.; Zhou, Y.; Jin, T. NLRP inflammasomes in health and disease. *Mol. Biomed.* **2024**, *5*, 14. [CrossRef] [PubMed]
137. You, L.; Chen, J.; Liu, W.; Xiang, Q.; Luo, Z.; Wang, W.; Xu, W.; Wu, K.; Zhang, Q.; Liu, Y.; et al. Enterovirus 71 induces neural cell apoptosis and autophagy through promoting ACOX1 downregulation and ROS generation. *Virulence* **2020**, *11*, 537–553. [CrossRef] [PubMed]
138. Lei, X.; Liu, X.; Ma, Y.; Sun, Z.; Yang, Y.; Jin, Q.; He, B.; Wang, J. The 3C protein of enterovirus 71 inhibits retinoid acid-inducible gene I-mediated interferon regulatory factor 3 activation and type I interferon responses. *J. Virol.* **2010**, *84*, 8051–8061. [CrossRef] [PubMed]
139. Komaravelli, N.; Tian, B.; Ivanciuc, T.; Mautemps, N.; Brasier, A.R.; Garofalo, R.P.; Casola, A. Respiratory syncytial virus infection down-regulates antioxidant enzyme expression by triggering deacetylation-proteasomal degradation of Nrf2. *Free Radic. Biol. Med.* **2015**, *88*, 391–403. [CrossRef] [PubMed]
140. Elmore, S. Apoptosis: A Review of Programmed Cell Death. *Toxicol. Pathol.* **2016**, *35*, 495–516. [CrossRef] [PubMed]
141. Zhirnov, O.P.; Klenk, H.D. Control of apoptosis in influenza virus-infected cells by up-regulation of Akt and p53 signaling. *Apoptosis* **2007**, *12*, 1419–1432. [CrossRef]
142. Ampomah, P.B.; Lim, L.H.K. Influenza A virus-induced apoptosis and virus propagation. *Apoptosis* **2019**, *25*, 1–11. [CrossRef]
143. Liu, Y.; Garron, T.M.; Chang, Q.; Su, Z.; Zhou, C.; Qiu, Y.; Gong, E.C.; Zheng, J.; Yin, Y.W.; Ksiazek, T.; et al. Cell-Type Apoptosis in Lung during SARS-CoV-2 Infection. *Pathogens* **2021**, *10*, 509. [CrossRef]
144. Ren, Y.; Shu, T.; Wu, D.; Mu, J.; Wang, C.; Huang, M.; Han, Y.; Zhang, X.-Y.; Zhou, W.; Qiu, Y.; et al. The ORF3a protein of SARS-CoV-2 induces apoptosis in cells. *Cell. Mol. Immunol.* **2020**, *17*, 881–883. [CrossRef] [PubMed]
145. Yapasert, R.; Khaw-on, P.; Banjerdpongchai, R. Coronavirus Infection-Associated Cell Death Signaling and Potential Therapeutic Targets. *Molecules* **2021**, *26*, 7459. [CrossRef]
146. Li, L.; Wang, S.; Zhou, W. Balance Cell Apoptosis and Pyroptosis of Caspase-3-Activating Chemotherapy for Better Antitumor Therapy. *Cancers* **2022**, *15*, 26. [CrossRef]
147. Donia, A.; Bokhari, H. Apoptosis induced by SARS-CoV-2: Can we target it? *Apoptosis* **2021**, *26*, 7–8. [CrossRef]
148. Li, M.; Li, J.; Zeng, R.; Yang, J.; Liu, J.; Zhang, Z.; Song, X.; Yao, Z.; Ma, C.; Li, W.; et al. Respiratory Syncytial Virus Replication Is Promoted by Autophagy-Mediated Inhibition of Apoptosis. *J. Virol.* **2018**, *92*. [CrossRef]
149. Thomson, B.J. Viruses and apoptosis. *Int. J. Exp. Pathol.* **2001**, *82*, 65–76. [CrossRef] [PubMed]
150. Shen, Y.; Shenk, T.E. Viruses and apoptosis. *Curr. Opin. Genet. Dev.* **1995**, *5*, 105–111. [CrossRef] [PubMed]

151. Niture, S.K.; Jaiswal, A.K. Nrf2 protein up-regulates antiapoptotic protein Bcl-2 and prevents cellular apoptosis. *J. Biol. Chem.* **2012**, *287*, 9873–9886. [CrossRef]
152. Khan, N.M.; Ahmad, I.; Haqqi, T.M. Nrf2/ARE pathway attenuates oxidative and apoptotic response in human osteoarthritis chondrocytes by activating ERK1/2/ELK1-P70S6K-P90RSK signaling axis. *Free Radic. Biol. Med.* **2018**, *116*, 159–171. [CrossRef]
153. Bonay, M.; Roux, A.L.; Floquet, J.; Retory, Y.; Herrmann, J.L.; Lofaso, F.; Deramaudt, T.B. Caspase-independent apoptosis in infected macrophages triggered by sulforaphane via Nrf2/p38 signaling pathways. *Cell Death Discov.* **2015**, *1*, 15022. [CrossRef] [PubMed]
154. Kensler, T.W.; Egner, P.A.; Agyeman, A.S.; Visvanathan, K.; Groopman, J.D.; Chen, J.G.; Chen, T.Y.; Fahey, J.W.; Talalay, P. Keap1-nrf2 signaling: A target for cancer prevention by sulforaphane. *Nat. Prod. Cancer Prev. Ther.* **2013**, *329*, 163–177. [CrossRef] [PubMed]
155. Wang, H.; Jia, X.; Zhang, M.; Cheng, C.; Liang, X.; Wang, X.; Xie, F.; Wang, J.; Yu, Y.; He, Y.; et al. Isoliquiritigenin inhibits virus replication and virus-mediated inflammation via NRF2 signaling. *Phytomedicine* **2023**, *114*, 154786. [CrossRef] [PubMed]
156. Hassan, S.M.; Jawad, M.J.; Ahjel, S.W.; Singh, R.B.; Singh, J.; Awad, S.M.; Hadi, N.R. The Nrf2 Activator (DMF) and Covid-19: Is there a Possible Role? *Med. Arch.* **2020**, *74*, 134–138. [CrossRef] [PubMed]
157. Lurje, I.; Gaisa, N.T.; Weiskirchen, R.; Tacke, F. Mechanisms of organ fibrosis: Emerging concepts and implications for novel treatment strategies. *Mol. Asp. Med.* **2023**, *92*, 101191. [CrossRef] [PubMed]
158. Lee, J.H.; Park, H.J.; Kim, S.; Kim, Y.J.; Kim, H.C. Epidemiology and comorbidities in idiopathic pulmonary fibrosis: A nationwide cohort study. *BMC Pulm. Med.* **2023**, *23*, 54. [CrossRef] [PubMed]
159. Ley, B.; Collard, H.R. Epidemiology of idiopathic pulmonary fibrosis. *Clin. Epidemiol.* **2013**, *5*, 483–492. [CrossRef] [PubMed]
160. Kaul, B.; Lee, J.S.; Zhang, N.; Vittinghoff, E.; Sarmiento, K.; Collard, H.R.; Whooley, M.A. Epidemiology of Idiopathic Pulmonary Fibrosis among U.S. Veterans, 2010–2019. *Ann. Am. Thorac. Soc.* **2022**, *19*, 196–203. [CrossRef] [PubMed]
161. Harari, S.; Davi, M.; Biffi, A.; Caminati, A.; Ghirardini, A.; Lovato, V.; Cricelli, C.; Lapi, F. Epidemiology of idiopathic pulmonary fibrosis: A population-based study in primary care. *Intern. Emerg. Med.* **2020**, *15*, 437–445. [CrossRef]
162. Martinez, F.J.; Collard, H.R.; Pardo, A.; Raghu, G.; Richeldi, L.; Selman, M.; Swigris, J.J.; Taniguchi, H.; Wells, A.U. Idiopathic pulmonary fibrosis. *Nat. Rev. Dis. Primers* **2017**, *3*, 17074. [CrossRef]
163. Sheng, G.; Chen, P.; Wei, Y.; Yue, H.; Chu, J.; Zhao, J.; Wang, Y.; Zhang, W.; Zhang, H.-L. Viral Infection Increases the Risk of Idiopathic Pulmonary Fibrosis. *Chest* **2020**, *157*, 1175–1187. [CrossRef] [PubMed]
164. George, P.M.; Wells, A.U.; Jenkins, R.G. Pulmonary fibrosis and COVID-19: The potential role for antifibrotic therapy. *Lancet Respir. Med.* **2020**, *8*, 807–815. [CrossRef] [PubMed]
165. Wang, L.; Cheng, W.; Zhang, Z. Respiratory syncytial virus infection accelerates lung fibrosis through the unfolded protein response in a bleomycin-induced pulmonary fibrosis animal model. *Mol. Med. Rep.* **2017**, *16*, 310–316. [CrossRef] [PubMed]
166. Shieh, W.J.; Blau, D.M.; Denison, A.M.; Deleon-Carnes, M.; Adem, P.; Bhatnagar, J.; Sumner, J.; Liu, L.; Patel, M.; Batten, B.; et al. 2009 pandemic influenza A (H1N1): Pathology and pathogenesis of 100 fatal cases in the United States. *Am. J. Pathol.* **2010**, *177*, 166–175. [CrossRef] [PubMed]
167. Roberson, E.C.; Tully, J.E.; Guala, A.S.; Reiss, J.N.; Godburn, K.E.; Pociask, D.A.; Alcorn, J.F.; Riches, D.W.; Dienz, O.; Janssen-Heininger, Y.M.; et al. Influenza induces endoplasmic reticulum stress, caspase-12-dependent apoptosis, and c-Jun N-terminal kinase-mediated transforming growth factor-beta release in lung epithelial cells. *Am. J. Respir. Cell Mol. Biol.* **2012**, *46*, 573–581. [CrossRef] [PubMed]
168. Huang, W.J.; Tang, X.X. Virus infection induced pulmonary fibrosis. *J. Transl. Med.* **2021**, *19*, 496. [CrossRef]
169. Han, X.; Fan, Y.; Alwalid, O.; Li, N.; Jia, X.; Yuan, M.; Li, Y.; Cao, Y.; Gu, J.; Wu, H.; et al. Six-month Follow-up Chest CT Findings after Severe COVID-19 Pneumonia. *Radiology* **2021**, *299*, E177–E186. [CrossRef] [PubMed]
170. Kikuchi, N.; Ishii, Y.; Morishima, Y.; Yageta, Y.; Haraguchi, N.; Itoh, K.; Yamamoto, M.; Hizawa, N. Nrf2 protects against pulmonary fibrosis by regulating the lung oxidant level and Th1/Th2 balance. *Respir. Res.* **2010**, *11*, 1–12. [CrossRef] [PubMed]
171. Kim, B.; Kaistha, S.D.; Rouse, B.T. Viruses and autoimmunity. *Autoimmunity* **2009**, *39*, 71–77. [CrossRef] [PubMed]
172. Fujinami, R.S.; von Herrath, M.G.; Christen, U.; Whitton, J.L. Molecular Mimicry, Bystander Activation, or Viral Persistence: Infections and Autoimmune Disease. *Clin. Microbiol. Rev.* **2006**, *19*, 80–94. [CrossRef]
173. Shim, C.-H.; Cho, S.; Shin, Y.-M.; Choi, J.-M. Emerging role of bystander T cell activation in autoimmune diseases. *BMB Rep.* **2022**, *55*, 57–64. [CrossRef] [PubMed]
174. Lehman, H.K. Autoimmunity and Immune Dysregulation in Primary Immune Deficiency Disorders. *Curr. Allergy Asthma Rep.* **2015**, *15*, 53. [CrossRef] [PubMed]
175. Gibney, S.M.; Drexhage, H.A. Evidence for a Dysregulated Immune System in the Etiology of Psychiatric Disorders. *J. Neuroimmune Pharmacol.* **2013**, *8*, 900–920. [CrossRef] [PubMed]
176. Vanderlugt, C.L.; Miller, S.D. Epitope spreading in immune-mediated diseases: Implications for immunotherapy. *Nat. Rev. Immunol.* **2002**, *2*, 85–95. [CrossRef] [PubMed]
177. Mackay, I.R.; Rowley, M.J. Autoimmune epitopes: Autoepitopes. *Autoimmun. Rev.* **2004**, *3*, 487–492. [CrossRef] [PubMed]
178. Coppieters, K.T.; Wiberg, A.; von Herrath, M.G. Viral infections and molecular mimicry in type 1 diabetes. *Apmis* **2012**, *120*, 941–949. [CrossRef] [PubMed]

179. Smatti, M.K.; Cyprian, F.S.; Nasrallah, G.K.; Al Thani, A.A.; Almishal, R.O.; Yassine, H.M. Viruses and Autoimmunity: A Review on the Potential Interaction and Molecular Mechanisms. *Viruses* **2019**, *11*, 762. [CrossRef] [PubMed]
180. Rojas, M.; Restrepo-Jiménez, P.; Monsalve, D.M.; Pacheco, Y.; Acosta-Ampudia, Y.; Ramírez-Santana, C.; Leung, P.S.C.; Ansari, A.A.; Gershwin, M.E.; Anaya, J.-M. Molecular mimicry and autoimmunity. *J. Autoimmun.* **2018**, *95*, 100–123. [CrossRef] [PubMed]
181. Tan, H.; Wang, C.; Yu, Y. H1N1 Influenza: The Trigger of Diabetic Ketoacidosis in a Young Woman with Ketosis-Prone Diabetes. *Am. J. Med. Sci.* **2012**, *343*, 180–183. [CrossRef]
182. Watanabe, N. Conversion to type 1 diabetes after H1N1 influenza infection: A case report. *J. Diabetes* **2011**, *3*, 103. [CrossRef]
183. Lönnrot, M.; Lynch, K.F.; Elding Larsson, H.; Lernmark, Å.; Rewers, M.J.; Törn, C.; Burkhardt, B.R.; Briese, T.; Hagopian, W.A.; She, J.-X.; et al. Respiratory infections are temporally associated with initiation of type 1 diabetes autoimmunity: The TEDDY study. *Diabetologia* **2017**, *60*, 1931–1940. [CrossRef] [PubMed]
184. Durbin, J.E.; Durbin, R.K. Respiratory Syncytial Virus-Induced Immunoprotection and Immunopathology. *Viral Immunol.* **2004**, *17*, 370–380. [CrossRef] [PubMed]
185. Kocivnik, N.; Velnar, T. A Review Pertaining to SARS-CoV-2 and Autoimmune Diseases: What Is the Connection? *Life* **2022**, *12*, 1918. [CrossRef] [PubMed]
186. Dorward, D.A.; Russell, C.D.; Um, I.H.; Elshani, M.; Armstrong, S.D.; Penrice-Randal, R.; Millar, T.; Lerpiniere, C.E.B.; Tagliavini, G.; Hartley, C.S.; et al. Tissue-Specific Immunopathology in Fatal COVID-19. *Am. J. Respir. Crit. Care Med.* **2021**, *203*, 192–201. [CrossRef] [PubMed]
187. Sagy, I.; Zeller, L.; Raviv, Y.; Porges, T.; Bieber, A.; Abu-Shakra, M. New-onset systemic lupus erythematosus following BNT162b2 mRNA COVID-19 vaccine: A case series and literature review. *Rheumatol. Int.* **2022**, *42*, 2261–2266. [CrossRef] [PubMed]
188. Zebardast, A.; Hasanzadeh, A.; Ebrahimian Shiadeh, S.A.; Tourani, M.; Yahyapour, Y. COVID-19: A trigger of autoimmune diseases. *Cell Biol. Int.* **2023**, *47*, 848–858. [CrossRef] [PubMed]
189. Li, J.; Stein, T.D.; Johnson, J.A. Genetic dissection of systemic autoimmune disease in Nrf2-deficient mice. *Physiol. Genom.* **2004**, *18*, 261–272. [CrossRef] [PubMed]
190. Kavian, N.; Mehlal, S.; Jeljeli, M.; Saidu, N.E.B.; Nicco, C.; Cerles, O.; Chouzenoux, S.; Cauvet, A.; Camus, C.; Ait-Djoudi, M.; et al. The Nrf2-Antioxidant Response Element Signaling Pathway Controls Fibrosis and Autoimmunity in Scleroderma. *Front. Immunol.* **2018**, *9*, 1896. [CrossRef]
191. Cuadrado, A.; Manda, G.; Hassan, A.; Alcaraz, M.J.; Barbas, C.; Daiber, A.; Ghezzi, P.; León, R.; López, M.G.; Oliva, B.; et al. Transcription Factor NRF2 as a Therapeutic Target for Chronic Diseases: A Systems Medicine Approach. *Pharmacol. Rev.* **2018**, *70*, 348–383. [CrossRef]
192. Ma, Z.; Yang, K.Y.; Huang, Y.; Lui, K.O. Endothelial contribution to COVID-19: An update on mechanisms and therapeutic implications. *J. Mol. Cell. Cardiol.* **2022**, *164*, 69–82. [CrossRef]
193. Varga, Z.; Flammer, A.J.; Steiger, P.; Haberecker, M.; Andermatt, R.; Zinkernagel, A.S.; Mehra, M.R.; Schuepbach, R.A.; Ruschitzka, F.; Moch, H. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* **2020**, *395*, 1417–1418. [CrossRef] [PubMed]
194. Aid, M.; Busman-Sahay, K.; Vidal, S.J.; Maliga, Z.; Bondoc, S.; Starke, C.; Terry, M.; Jacobson, C.A.; Wrijil, L.; Ducat, S.; et al. Vascular Disease and Thrombosis in SARS-CoV-2-Infected Rhesus Macaques. *Cell* **2020**, *183*, 1354–1366.e1313. [CrossRef] [PubMed]
195. Canham, S.M.; Wang, Y.; Cornett, A.; Auld, D.S.; Baeschlin, D.K.; Patoor, M.; Skaanderup, P.R.; Honda, A.; Llamas, L.; Wendel, G.; et al. Systematic Chemogenetic Library Assembly. *Cell Chem. Biol.* **2020**, *27*, 1124–1129. [CrossRef] [PubMed]
196. Bikdeli, B.; Madhavan, M.V.; Jimenez, D.; Chuich, T.; Dreyfus, I.; Driggin, E.; Nigoghossian, C.D.; Ageno, W.; Madjid, M.; Guo, Y.; et al. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up. *J. Am. Coll. Cardiol.* **2020**, *75*, 2950–2973. [CrossRef] [PubMed]
197. Armstrong, S.M.; Darwish, I.; Lee, W.L. Endothelial activation and dysfunction in the pathogenesis of influenza A virus infection. *Virulence* **2014**, *4*, 537–542. [CrossRef] [PubMed]
198. Wang, S.; Le, T.Q.; Kurihara, N.; Chida, J.; Cisse, Y.; Yano, M.; Kido, H. Influenza Virus–Cytokine-Protease Cycle in the Pathogenesis of Vascular Hyperpermeability in Severe Influenza. *J. Infect. Dis.* **2010**, *202*, 991–1001. [CrossRef] [PubMed]
199. Kanwugu, O.N.; Glukhareva, T.V. Activation of Nrf2 pathway as a protective mechanism against oxidative stress-induced diseases: Potential of astaxanthin. *Arch. Biochem. Biophys.* **2023**, *741*, 109601. [CrossRef] [PubMed]
200. Huang, Z.; Wu, M.; Zeng, L.; Wang, D.; Sun, J. The Beneficial Role of Nrf2 in the Endothelial Dysfunction of Atherosclerosis. *Cardiol. Res. Pract.* **2022**, *2022*, 4287711. [CrossRef]
201. Florczyk, U.; Jazwa, A.; Maleszewska, M.; Mendel, M.; Szade, K.; Kozakowska, M.; Grochot-Przeczek, A.; Viscardi, M.; Czauderna, S.; Bukowska-Strakova, K.; et al. Nrf2 Regulates Angiogenesis: Effect on Endothelial Cells, Bone Marrow-Derived Proangiogenic Cells and Hind Limb Ischemia. *Antioxid. Redox Signal.* **2014**, *20*, 1693–1708. [CrossRef]
202. Vashi, R.; Patel, B.M. NRF2 in Cardiovascular Diseases: A Ray of Hope! *J. Cardiovasc. Transl. Res.* **2020**, *14*, 573–586. [CrossRef]
203. Satta, S.; Mahmoud, A.M.; Wilkinson, F.L.; Yvonne Alexander, M.; White, S.J. The Role of Nrf2 in Cardiovascular Function and Disease. *Oxid. Med. Cell. Longev.* **2017**, *2017*, 9237263. [CrossRef] [PubMed]

204. Mirza, M.A.I.; Alsiö, J.; Hammarstedt, A.; Erben, R.G.; Michaëlsson, K.; Tivesten, Å.; Marsell, R.; Orwoll, E.; Karlsson, M.K.; Ljunggren, Ö.; et al. Circulating Fibroblast Growth Factor-23 Is Associated with Fat Mass and Dyslipidemia in Two Independent Cohorts of Elderly Individuals. *Arterioscler. Thromb. Vasc. Biol.* **2011**, *31*, 219–227. [CrossRef] [PubMed]
205. Daskou, M.; Fotooh Abadi, L.; Gain, C.; Wong, M.; Sharma, E.; Kombe Kombe, A.J.; Nanduri, R.; Kelesidis, T. The Role of the NRF2 Pathway in the Pathogenesis of Viral Respiratory Infections. *Pathogens* **2023**, *13*, 39. [CrossRef] [PubMed]
206. Pokharel, S.M.; Shil, N.K.; Bose, S. Autophagy, TGF-beta, and SMAD-2/3 Signaling Regulates Interferon-beta Response in Respiratory Syncytial Virus Infected Macrophages. *Front. Cell Infect. Microbiol.* **2016**, *6*, 174. [CrossRef] [PubMed]
207. Ribo-Molina, P.; Weiss, H.J.; Susma, B.; van Nieuwkoop, S.; Persoons, L.; Zheng, Y.; Ruzek, M.; Daelemans, D.; Fouchier, R.A.M.; O'Neill, L.A.J.; et al. 4-Octyl itaconate reduces influenza A replication by targeting the nuclear export protein CRM1. *J. Virol.* **2023**, *97*, e0132523. [CrossRef] [PubMed]
208. Sohail, A.; Iqbal, A.A.; Sahini, N.; Chen, F.; Tantawy, M.; Waqas, S.F.H.; Winterhoff, M.; Ebensen, T.; Schultz, K.; Geffers, R.; et al. Correction: Itaconate and derivatives reduce interferon responses and inflammation in influenza A virus infection. *PLoS Pathog.* **2022**, *18*, e1011002. [CrossRef] [PubMed]
209. Dai, J.; Gu, L.; Su, Y.; Wang, Q.; Zhao, Y.; Chen, X.; Deng, H.; Li, W.; Wang, G.; Li, K. Inhibition of curcumin on influenza A virus infection and influenzal pneumonia via oxidative stress, TLR2/4, p38/JNK MAPK and NF-kappaB pathways. *Int. Immunopharmacol.* **2018**, *54*, 177–187. [CrossRef]
210. Chen, T.Y.; Chen, D.Y.; Wen, H.W.; Ou, J.L.; Chiou, S.S.; Chen, J.M.; Wong, M.L.; Hsu, W.L. Inhibition of enveloped viruses infectivity by curcumin. *PLoS ONE* **2013**, *8*, e62482. [CrossRef]
211. Fukuyama, S.; Kawaoka, Y. The pathogenesis of influenza virus infections: The contributions of virus and host factors. *Curr. Opin. Immunol.* **2011**, *23*, 481–486. [CrossRef]
212. Jobe, A.H.; Ikegami, M. Mechanisms initiating lung injury in the preterm. *Early Hum. Dev.* **1998**, *53*, 81–94. [CrossRef]
213. Mostafa, A.; Mostafa-Hedeab, G.; Elhady, H.A.; Mohamed, E.A.; Eledrdery, A.Y.; Alruwaili, S.H.; Al-Abd, A.M.; Allayeh, A.K. Dual action of epigallocatechin-3-gallate in virus-induced cell Injury. *J. Genet. Eng. Biotechnol.* **2023**, *21*, 145. [CrossRef] [PubMed]
214. Yageta, Y.; Ishii, Y.; Morishima, Y.; Ano, S.; Ohtsuka, S.; Matsuyama, M.; Takeuchi, K.; Itoh, K.; Yamamoto, M.; Hizawa, N. Carbocisteine reduces virus-induced pulmonary inflammation in mice exposed to cigarette smoke. *Am. J. Respir. Cell Mol. Biol.* **2014**, *50*, 963–973. [CrossRef] [PubMed]
215. Wang, W.; Guan, W.J.; Huang, R.Q.; Xie, Y.Q.; Zheng, J.P.; Zhu, S.X.; Chen, M.; Zhong, N.S. Carbocisteine attenuates TNF-alpha-induced inflammation in human alveolar epithelial cells in vitro through suppressing NF-kappaB and ERK1/2 MAPK signaling pathways. *Acta Pharmacol. Sin.* **2016**, *37*, 629–636. [CrossRef] [PubMed]
216. Cancer Genome Atlas Research Network. Comprehensive genomic characterization of squamous cell lung cancers. *Nature* **2012**, *489*, 519–525. [CrossRef] [PubMed]
217. Cho, H.Y.; van Houten, B.; Wang, X.; Miller-DeGraff, L.; Fostel, J.; Gladwell, W.; Perrow, L.; Panduri, V.; Kobzik, L.; Yamamoto, M.; et al. Targeted deletion of nrf2 impairs lung development and oxidant injury in neonatal mice. *Antioxid. Redox Signal.* **2012**, *17*, 1066–1082. [CrossRef] [PubMed]
218. Liu, Q.; Gao, Y.; Ci, X. Role of Nrf2 and Its Activators in Respiratory Diseases. *Oxid. Med. Cell Longev.* **2019**, *2019*, 7090534. [CrossRef] [PubMed]
219. Houghton, C.A.; Fassett, R.G.; Coombes, J.S. Sulforaphane and Other Nutrigenomic Nrf2 Activators: Can the Clinician's Expectation Be Matched by the Reality? *Oxid. Med. Cell Longev.* **2016**, *2016*, 7857186. [CrossRef] [PubMed]
220. Noah, T.L.; Zhang, H.; Zhou, H.; Glista-Baker, E.; Muller, L.; Bauer, R.N.; Meyer, M.; Murphy, P.C.; Jones, S.; Letang, B.; et al. Effect of broccoli sprouts on nasal response to live attenuated influenza virus in smokers: A randomized, double-blind study. *PLoS ONE* **2014**, *9*, e98671. [CrossRef] [PubMed]
221. Ordonez, A.A.; Bullen, C.K.; Villabona-Rueda, A.F.; Thompson, E.A.; Turner, M.L.; Merino, V.F.; Yan, Y.; Kim, J.; Davis, S.L.; Komm, O.; et al. Sulforaphane exhibits antiviral activity against pandemic SARS-CoV-2 and seasonal HCoV-OC43 coronaviruses in vitro and in mice. *Commun. Biol.* **2022**, *5*, 242. [CrossRef] [PubMed]
222. Qian, J.; Ma, X.; Xun, Y.; Pan, L. Protective effect of forsythiaside A on OVA-induced asthma in mice. *Eur. J. Pharmacol.* **2017**, *812*, 250–255. [CrossRef]
223. Mangla, B.; Javed, S.; Sultan, M.H.; Kumar, P.; Kohli, K.; Najmi, A.; Alhazmi, H.A.; Al Bratty, M.; Ahsan, W. Sulforaphane: A review of its therapeutic potentials, advances in its nanodelivery, recent patents, and clinical trials. *Phytother. Res.* **2021**, *35*, 5440–5458. [CrossRef] [PubMed]
224. Cho, H.Y. Genomic structure and variation of nuclear factor (erythroid-derived 2)-like 2. *Oxid. Med. Cell Longev.* **2013**, *2013*, 286524. [CrossRef] [PubMed]
225. Reddy, N.M.; Suryanaraya, V.; Yates, M.S.; Kleeberger, S.R.; Hassoun, P.M.; Yamamoto, M.; Liby, K.T.; Sporn, M.B.; Kensler, T.W.; Reddy, S.P. The triterpenoid CDDO-imidazolide confers potent protection against hyperoxic acute lung injury in mice. *Am. J. Respir. Crit. Care Med.* **2009**, *180*, 867–874. [CrossRef] [PubMed]
226. Harvey, C.J.; Thimmulappa, R.K.; Sethi, S.; Kong, X.; Yarmus, L.; Brown, R.H.; Feller-Kopman, D.; Wise, R.; Biswal, S. Targeting Nrf2 signaling improves bacterial clearance by alveolar macrophages in patients with COPD and in a mouse model. *Sci. Transl. Med.* **2011**, *3*, 78ra32. [CrossRef] [PubMed]

227. Cui, W.; Zhang, Z.; Zhang, P.; Qu, J.; Zheng, C.; Mo, X.; Zhou, W.; Xu, L.; Yao, H.; Gao, J. Nrf2 attenuates inflammatory response in COPD/emphysema: Crosstalk with Wnt3a/beta-catenin and AMPK pathways. *J. Cell Mol. Med.* **2018**, *22*, 3514–3525. [CrossRef] [PubMed]
228. Guerra, A.; Parhiz, H.; Rivella, S. Novel potential therapeutics to modify iron metabolism and red cell synthesis in diseases associated with defective erythropoiesis. *Haematologica* **2023**, *108*, 2582–2593. [CrossRef] [PubMed]
229. Bou-Fakhredin, R.; De Franceschi, L.; Motta, I.; Eid, A.A.; Taher, A.T.; Cappellini, M.D. Redox Balance in beta-Thalassemia and Sickle Cell Disease: A Love and Hate Relationship. *Antioxidants* **2022**, *11*, 967. [CrossRef] [PubMed]
230. Mbiandjeu, S.C.T.; Siciliano, A.; Matte, A.; Federti, E.; Perduca, M.; Melisi, D.; Andolfo, I.; Amoresano, A.; Iolascon, A.; Valenti, M.T.; et al. Nrf2 Plays a Key Role in Erythropoiesis during Aging. *Antioxidants* **2024**, *13*, 454. [CrossRef] [PubMed]
231. Qi, C.; Liu, X.; Xiong, T.; Wang, D. Tempol prevents isoprenaline-induced takotsubo syndrome via the reactive oxygen species/mitochondrial/anti-apoptosis/p38 MAPK pathway. *Eur. J. Pharmacol.* **2020**, *886*, 173439. [CrossRef] [PubMed]
232. Xu, R.; Yuan, L.S.; Gan, Y.Q.; Lu, N.; Li, Y.P.; Zhou, Z.Y.; Hu, B.; Wong, T.S.; He, X.H.; Zha, Q.B.; et al. Extracellular ATP contributes to the reactive oxygen species burst and exaggerated mitochondrial damage in D-galactosamine and lipopolysaccharide-induced fulminant hepatitis. *Int. Immunopharmacol.* **2024**, *130*, 111680. [CrossRef]
233. Han, X.; Hong, Q.; Peng, F.; Zhang, Y.; Wu, L.; Wang, X.; Zheng, Y.; Chen, X. Hippo pathway activated by circulating reactive oxygen species mediates cardiac diastolic dysfunction after acute kidney injury. *Biochim. Biophys. Acta Mol. Basis Dis.* **2024**, *1870*, 167184. [CrossRef] [PubMed]
234. Li, B.; Wang, Y.; Jiang, X.; Du, H.; Shi, Y.; Xiu, M.; Liu, Y.; He, J. Natural products targeting Nrf2/ARE signaling pathway in the treatment of inflammatory bowel disease. *Biomed. Pharmacother.* **2023**, *164*, 114950. [CrossRef] [PubMed]
235. Piotrowska, M.; Swierczynski, M.; Fichna, J.; Piechota-Polanczyk, A. The Nrf2 in the pathophysiology of the intestine: Molecular mechanisms and therapeutic implications for inflammatory bowel diseases. *Pharmacol. Res.* **2021**, *163*, 105243. [CrossRef] [PubMed]
236. Jo, D.; Arjunan, A.; Choi, S.; Jung, Y.S.; Park, J.; Jo, J.; Kim, O.Y.; Song, J. Oligonol ameliorates liver function and brain function in the 5 x FAD mouse model: Transcriptional and cellular analysis. *Food Funct.* **2023**, *14*, 9650–9670. [CrossRef] [PubMed]
237. Kim, J.; Lee, J.Y.; Kim, C.Y. A Comprehensive Review of Pathological Mechanisms and Natural Dietary Ingredients for the Management and Prevention of Sarcopenia. *Nutrients* **2023**, *15*, 2625. [CrossRef] [PubMed]
238. Silva, D.A.D.; Correia, T.M.L.; Pereira, R.; da Silva, R.A.A.; Augusto, O.; Queiroz, R.F. Tempol reduces inflammation and oxidative damage in cigarette smoke-exposed mice by decreasing neutrophil infiltration and activating the Nrf2 pathway. *Chem. Biol. Interact.* **2020**, *329*, 109210. [CrossRef] [PubMed]
239. Benedetti, F.; Sorrenti, V.; Buriani, A.; Fortinguerra, S.; Scapagnini, G.; Zella, D. Resveratrol, Rapamycin and Metformin as Modulators of Antiviral Pathways. *Viruses* **2020**, *12*, 1458. [CrossRef] [PubMed]
240. Jayasuriya, R.; Dhamodharan, U.; Ali, D.; Ganesan, K.; Xu, B.; Ramkumar, K.M. Targeting Nrf2/Keap1 signaling pathway by bioactive natural agents: Possible therapeutic strategy to combat liver disease. *Phytomedicine* **2021**, *92*, 153755. [CrossRef]
241. Thiruvengadam, M.; Venkidasamy, B.; Subramanian, U.; Samynathan, R.; Ali Shariati, M.; Rebezov, M.; Girish, S.; Thangavel, S.; Dhanapal, A.R.; Fedoseeva, N.; et al. Bioactive Compounds in Oxidative Stress-Mediated Diseases: Targeting the NRF2/ARE Signaling Pathway and Epigenetic Regulation. *Antioxidants* **2021**, *10*, 1859. [CrossRef] [PubMed]
242. Gugliandolo, A.; Bramanti, P.; Mazzon, E. Activation of Nrf2 by Natural Bioactive Compounds: A Promising Approach for Stroke? *Int. J. Mol. Sci.* **2020**, *21*, 4875. [CrossRef]
243. Krajka-Kuzniak, V.; Baer-Dubowska, W. Modulation of Nrf2 and NF-kappaB Signaling Pathways by Naturally Occurring Compounds in Relation to Cancer Prevention and Therapy. Are Combinations Better Than Single Compounds? *Int. J. Mol. Sci.* **2021**, *22*, 8223. [CrossRef] [PubMed]
244. Moratilla-Rivera, I.; Sánchez, M.; Valdés-González, J.A.; Gómez-Serranillos, M.P. Natural Products as Modulators of Nrf2 Signaling Pathway in Neuroprotection. *Int. J. Mol. Sci.* **2023**, *24*, 3748. [CrossRef] [PubMed]
245. Singh, S.; Nagalakshmi, D.; Sharma, K.K.; Ravichandiran, V. Natural antioxidants for neuroinflammatory disorders and possible involvement of Nrf2 pathway: A review. *Heliyon* **2021**, *7*, e06216. [CrossRef] [PubMed]
246. Checconi, P.; De Angelis, M.; Marcocci, M.E.; Fraternale, A.; Magnani, M.; Palamara, A.T.; Nencioni, L. Redox-Modulating Agents in the Treatment of Viral Infections. *Int. J. Mol. Sci.* **2020**, *21*, 4084. [CrossRef] [PubMed]
247. Chen, X.; Song, X.; Zhao, X.; Zhang, Y.; Wang, Y.; Jia, R.; Zou, Y.; Li, L.; Yin, Z. Insights into the Anti-inflammatory and Antiviral Mechanisms of Resveratrol. *Mediat. Inflamm.* **2022**, *2022*, 7138756. [CrossRef] [PubMed]
248. Hosseini, S.A.; Zahedipour, F.; Sathyapalan, T.; Jamialahmadi, T.; Sahebkar, A. Pulmonary fibrosis: Therapeutic and mechanistic insights into the role of phytochemicals. *Biofactors* **2021**, *47*, 250–269. [CrossRef] [PubMed]
249. Thimmulappa, R.K.; Mudnakudu-Nagaraju, K.K.; Shivamallu, C.; Subramaniam, K.J.T.; Radhakrishnan, A.; Bhojraj, S.; Kuppusamy, G. Antiviral and immunomodulatory activity of curcumin: A case for prophylactic therapy for COVID-19. *Heliyon* **2021**, *7*, e06350. [CrossRef] [PubMed]
250. Patel, S.S.; Acharya, A.; Ray, R.S.; Agrawal, R.; Raghuwanshi, R.; Jain, P. Cellular and molecular mechanisms of curcumin in prevention and treatment of disease. *Crit. Rev. Food Sci. Nutr.* **2020**, *60*, 887–939. [CrossRef] [PubMed]
251. Baranwal, M.; Gupta, Y.; Dey, P.; Majaw, S. Antiinflammatory phytochemicals against virus-induced hyperinflammatory responses: Scope, rationale, application, and limitations. *Phytother. Res.* **2021**, *35*, 6148–6169. [CrossRef]

252. Waqas, M.; Ullah, S.; Halim, S.A.; Rehman, N.U.; Ali, A.; Jan, A.; Muhsinah, A.B.; Khan, A.; Al-Harrasi, A. Targeting papain-like protease by natural products as novel therapeutic potential SARS-CoV-2. *Int. J. Biol. Macromol.* **2024**, *258*, 128812. [CrossRef]
253. Safari, A.; Khodabandeh, Z.; Borhani-Haghighi, A. Dimethyl Fumarate Can Enhance the Potential Therapeutic Effects of Epidermal Neural Crest Stem Cells in COVID-19 Patients. *Stem. Cell Rev. Rep.* **2021**, *17*, 300–301. [CrossRef] [PubMed]
254. Waqas, F.H.; Shehata, M.; Elgaher, W.A.M.; Lacour, A.; Kurmasheva, N.; Begnini, F.; Kiib, A.E.; Dahlmann, J.; Chen, C.; Pavlou, A.; et al. NRF2 activators inhibit influenza A virus replication by interfering with nucleo-cytoplasmic export of viral RNPs in an NRF2-independent manner. *PLoS Pathog.* **2023**, *19*, e1011506. [CrossRef] [PubMed]

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