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REVIEW

The roles of signaling pathways in SARS-CoV-2 infection; lessons learned from SARS-CoV and MERS-CoV

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Abstract

The number of descriptions of emerging viruses has grown at an unprecedented rate since the beginning of the 21st century. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), is the third highly pathogenic coronavirus that has introduced itself into the human population in the current era, after SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV). Molecular and cellular studies of the pathogenesis of this novel coronavirus are still in the early stages of research; however, based on similarities of SARS-CoV-2 to other coronaviruses, it can be hypothesized that the NF-κB, cytokine regulation, ERK, and TNF-α signaling pathways are the likely causes of inflammation at the onset of COVID-19. Several drugs have been prescribed and used to alleviate the adverse effects of these inflammatory cellular signaling pathways, and these might be beneficial for developing novel therapeutic modalities against COVID-19. In this review, we briefly summarize alterations of cellular signaling pathways that are associated with coronavirus infection, particularly SARS-CoV and MERS-CoV, and tabulate the therapeutic agents that are currently approved for treating other human diseases.

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Introduction

The number of descriptions of emerging viruses has grown at an unprecedented rate since the beginning of the 21st century [1, 2]. More than 100 years after the start of the 1918 influenza pandemic, we are now experiencing another pandemic. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has emerged as the third highly pathogenic coronavirus to introduce itself into the human population in the current era, after SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) [2]. The advent of SARS-CoV in 2002-2003 in China [3] and of MERS-CoV in the Kingdom of Saudi Arabia in 2012 [4] provoked general concern about their possible threat to global health security. SARS-CoV spread to several countries, with more than 8000 cases and more than 750 deaths [5, 6]. MERS-CoV infections have resulted in more than 600 deaths and caused severe respiratory disease in more than 1600 people [7, 8]. Numerous similarities and differences in the epidemiology, clinical properties, and handling of SARS and MERS have been recognized [9].

Viruses, including coronaviruses, manipulate the host cell machinery in order to complete their replication cycle [10].

Interfering with signaling pathways that regulate processes such as DNA repair and replication, immune response, transcription, metabolism, cell cycle, and survival is one of the ways for the virus to take over cellular processes [11]. Alteration of various signaling pathways involved in the central physiological functions of the cell takes place after coronavirus infection [12]. According to recent research reports, the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT), interferon, p38 mitogen-activated protein kinase (MAPK), epidermal growth factor receptor (EGFR), and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathways are altered following virus infection. These pathways are involved in antagonizing the host antiviral response and are vital for viral replication, entry, propagation, and apoptosis. Coronaviruses manipulate the molecular function of signaling pathways, and this kind of interaction between the host cell and the virus might be responsible for viral pathogenesis [13, 14].

Rapid intervention in the usual public-health behaviors and the development of antiviral compounds, antibodies, or vaccines are the keys to controlling the spread of a new virus and associated disease. MERS-CoV, SARS-CoV, and SARS-CoV-2 are betacoronaviruses share many characteristics but exhibit significant differences in their epidemiology, pathology, genetics, and protein composition. SARS-CoV-2 has around 79% genome sequence identity to SARS-CoV and nearly 50% to MERS-CoV [15, 16]. Because of these similarities, prior information about controlling SARS-CoV and MERS-CoV can serve as a guide to the pathogenesis and epidemiology of SARS-CoV-2 and to the improvement of therapeutic approaches to preventing viral infection.

This review provides a comparative overview of MERS-CoV, SARS-CoV, and the recently emerged SARS-CoV-2 in the interest of increasing understanding host-pathogen interactions, signaling pathways of the host, and immune evasion mechanisms by the pathogen that may be of use for the planning of new treatments for COVID-19.

Coronavirus structure and life cycle

Tyrrell and Bynoe reported the isolation of a virus from the respiratory tracts of adults with symptoms of the common cold. This virus was shown to have the ability to grow in human embryonic tracheal tissue culture and to induce cold symptoms when inoculated into healthy volunteers [17]. During the same period, Hamre and Procknown showed that an unknown virus obtained from samples taken from medical students complaining of cold symptoms could persist and infect tissue culture. These two unknown viruses were shown to be of the same type and named 229E [18]. These two novel respiratory viruses did not have the well-known properties of orthomyxoviruses or paramyxoviruses. They both had prominent crown-like extramembrane projections that were observed by electron microscopy and reported by Almeida and Tyrrell [19]. Subsequent comparison of these viruses to other contemporaneously discovered viruses, including infectious bronchitis virus, transmissible gastroenteritis virus of swine, and mouse hepatitis virus (MHV), led to the establishment of a new viral group named "coronavirus", in reference to their crown-like surface projections [20]. In the meantime, numerous coronaviruses have been identified, seven of which contribute to human diseases, with clinical expression ranging from asymptomatic or mild to lethal infections. Taxonomically, these viruses belong to the order *Nidovirales*, the family *Coronaviridae,* and the subfamily *Coronavirinae*, which is further divided into the genera *Alphacoronavirus, Betacoronavirus, Gammacoronavirus,* and *Deltacoronavirus* (International Committee on Taxonomy of Viruses [ICTV]). These genera include several viruses with the ability to infect human cells, and especially epithelial cells. Human coronaviruses (HCoV) belonging to the genera *Alphacoronavirus* and *Betacoronavirus* include HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1, which induce mild pathology in most cases, and SARS-CoV [21], MERS-CoV [22], and the causative agent of the new pandemic COVID-19, SARS-CoV-2 [23], which can induce severe syndromes. SARS-CoV-2 and SARS-CoV both belong to the subgenus *Sarbecovirus* of the genus *Betacoronavirus,* which also has four other subgenera: *Merbecovirus* (MERS-CoV), *Nobecovirus*, *Embecovirus* (HCoV-HKU1, MHV, HCoV-OC43, HCoV-B814), and *Hibecovirus*.

The coronavirus particle exhibits a pleomorphic spherical enveloped shape displaying a crown-like surface due to the presence of club-shaped spike (S) proteins (Fig. 1). In comparison to the other RNA viruses, this virus is large (approximately 120 nm in diameter) and possesses a single-stranded, positive-sense, helical RNA genome associated with nucleocapsid (N) proteins [24]. In addition to its role in assembly, the N protein can regulate coronavirus replication and the infected-cell response [25]. The next layer of the coronavirus particle contains the major structural proteins or so-called membrane (M) proteins, which function to stabilize and maintain the viral envelope. The last structural protein, the envelope (E) protein, is the smallest one and is abundantly expressed in coronavirus-infected cell, which contrasts with its low abundance in the virion itself [26]. The coronavirus genomic RNA, which ranges in size from 26.4 to 31.7 kb, contains genes coding for structural and non-structural proteins. The genome is organized as follows: 5'-leader-UTR-replicase/transcriptase-S-E-M-N-UTR-3'-poly(A) tail. The replicase gene encodes the non-structural proteins that are required for viral replication and completion of the viral life cycle [27].

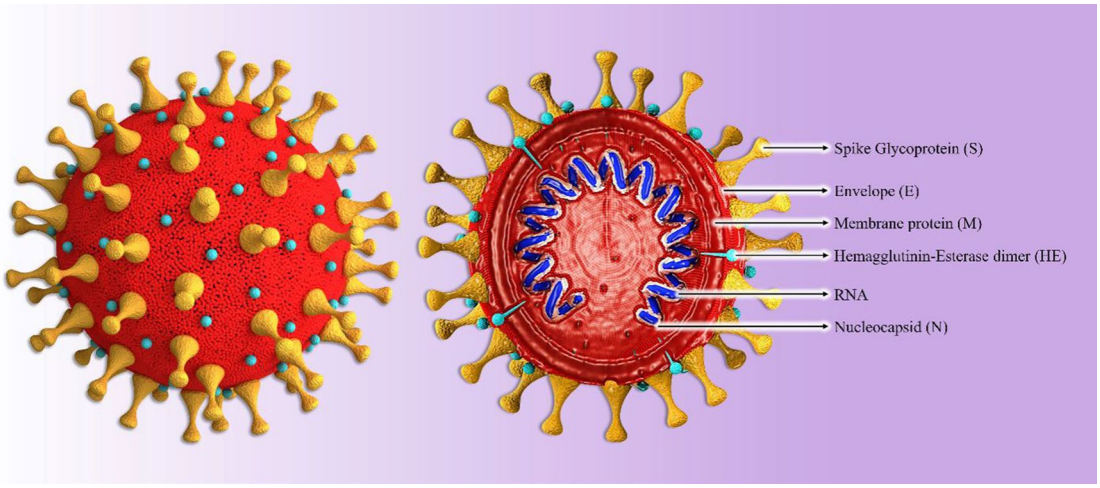

Fig. 1 The structure of a typical SARS-CoV-2 virion. The presence of the viral S protein gives a crown-like shape to the virion. The helical ssRNA is encapsidated with the N protein, and together they are covered by the E protein. There are several HE proteins on the surface of virion as well as spikes. The complete coronavirus virion has the capability to infect its target cells.

The coronavirus replication cycle starts with binding of the S protein to its receptor on the host cell via the receptor-binding domain (RBD). The interaction of S and the receptor determines not only which species can be infected but also which tissues can be involved in this infection [28]. The most abundant receptors used by coronaviruses are peptidases, and it has been shown that this binding is independent of the enzymatic domains of these peptidases. The receptor utilized by alphacoronaviruses such as HCoV-229E is usually aminopeptidase N (APN) [29], which is an enzyme that mostly functions during the immune response and oncogenesis and is involved in the antigen-presenting process [30], while angiotensin-converting enzyme 2 (ACE2), which could be involved in several pathological conditions, such as diabetes in pregnancy and related lung diseases [31], is the main receptor used by HCoV-NL63 [32], SARS-CoV [33], and the newly discovered SARS-CoV-2 [34]. CEACAM1 (carcinoembryonic antigen-related cell adhesion molecule 1) is employed during the entry stage of MHV infection [35], and MERS-CoV attaches to its host cell via binding to dipeptidyl peptidase 4 (DPP4) [36]. The next step in a coronavirus infection is the entry of the virus into the host cell, mediated by S protein cleavage via the activation of cathepsin, transmembrane serine protease 2 (TMPRSS2), or another protease in an acid-dependent manner, resulting in fusion of the viral membrane with the host cell membrane and the release of viral RNA into the cytosol (Fig. 2) [37]. The viral genomic RNA recruits the protein-production machinery of the host cell to translate the replicase-encoding region, which has two open reading frames (ORFs), rep1a (ORF1a), and rep1b (ORF1ab), to produce two polyproteins called pp1a and pp1ab. All of the non-structural proteins (nsps) are derived from these polyproteins. pp1a and pp1ab cleavage results in the production of nsp1-11 and nsp1-16, respectively [38]. The cleavage of polyproteins is mainly carried out by viral proteases encoded in the coronavirus RNA, including the papain-like protease (PLpro), produced from nsp3, and Mpro, produced from nsp5. MERS-CoV, SARS-CoV, and SARS-CoV-2 express only one type of PLpro, whereas the other expresses two types [39, 40]. In addition to the direct translation of the replicase gene and the production of nsps to initiate replication and transcription of structural proteins, the viral RNA is used as a template for the synthesis of genomic RNA for the formation of the complete virion and subgenomic RNA, which is translated into the coronavirus structural proteins E, S, and M, which are transmitted to endoplasmic reticulum (ER) and then extracted from the ER system into the ER-Golgi intermediate compartment (ERGIC) [41]. This kind of endosome is now ready for the incorporation of the encapsidated viral genomic RNA, producing and releasing a mature virion from the infected cell. For this purpose, the N protein is translated from a subgenomic RNA joining the newly synthesized viral genomic RNA and budding within the ERGIC [24]. Eventually, the mature virion is transported to the cell surface and released via exocytosis. Replication of the viral RNA produces double-stranded RNA intermediates, which are potent activators of host **??**pattern recognition receptors**??** (PRRs) especially since replication occurs in host-cell-membrane-containing replication complexes called double-membrane vesicles or viral replication organelles (ROs), which were previously shown to be recruited by SARS-CoV and MERS-CoV [42].

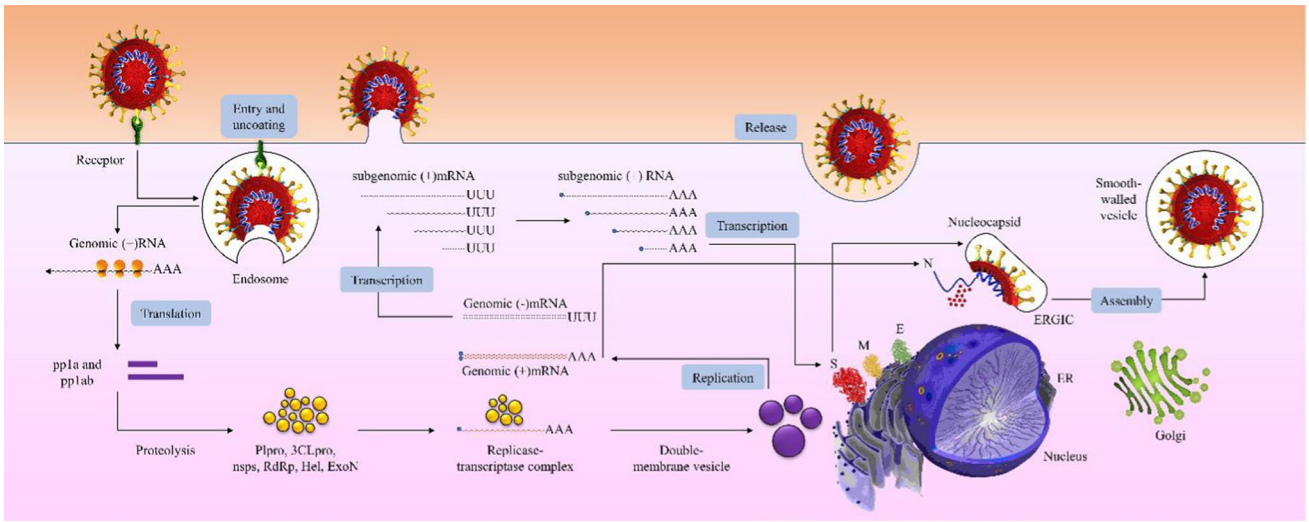

Fig. 2 Replication and transcription of SARS-CoV-2. The life cycle of the virus is initiated when a virion binds to its receptor, and this event is followed by entry into the host cell and uncoating, translation of the replicase gene, and synthesis of the pp1a and pp1ab polyproteins. After production of the viral structural proteins S, M, and E, the genomic RNA is encapsulated by N protein budding into the ERGIC, which finally gives rise to the release of the complete virion from the host cell.

Coronavirus and host molecular modifications

NF-κB

NF-κB is an important family of transcription factors that can enhance the transcription of stress-response proteins and pro-inflammatory cytokines and chemokines. In the cytoplasm, inhibitor of κB (IκB) binds to NF-κB and causes its inactivation [43]. Cellular stimuli trigger the degradation, ubiquitination, and phosphorylation of IκB through the proteasome and induce NF-κB translocation. NF-κB activation plays a crucial role in the inflammatory response against respiratory viruses such as human coronaviruses [44]. It has been reported that several structural and non-structural proteins of SARS-CoV, including the N protein, S protein, nsp1, nsp3a, and nsp7a, can stimulate NF-κB activation [45]. NF-κB is activated following rSARS-CoVMA15- E and rSARS-CoV-MA15 infection in cell culture and *in vivo* and also regulates the expression of proinflammatory mediators such as tumor necrosis factor (TNF), CCL2, and CXCL2. Therefore, inhibition of NF-κB by CAPE and parthenolide increases the survival of mice after infection and reduces the expression of pro-inflammatory cytokines in the lungs [45]. As a response to SARS-CoV infection, which is a stress-inducing condition, enhanced secretion of interleukin (IL)-1β is needed, which is done through two pathways, cleavage of pro-IL-1β and stimulation of pro-IL-1β transcription. The elevated level of IL-1β, in turn, increases the expression of several pro-inflammatory cytokines such as TNF-α and IL-6, followed by the activation of inflammasomes [46].

Regarding the ability of NLRP3 (NLR family pyrin domain containing 3) to facilitate the oligomerization of apoptosis-associated speck-like protein containing CARD (ASC) and to activate inflammasomes, SARS-CoV E protein, ORF3a, and ORF8b have been shown to be activators of NLRP3 inflammasomes. ORF3a and the E protein can induce the NF-κB activation required for pro-IL-1β gene transcription. In addition, the E protein, through Ca^{2+} transport, causes activation of NLRP3 inflammasomes [47]. SARS-CoV ORF3a accomplishes these phenomena through TNF receptor-associated factor 3 (TRAF3)-dependent ubiquitination of p105. Moreover, different mechanisms allow SARS-CoV ORF3a to promote assembly of NLRP3 inflammasomes via TRAF3-dependent ku3 ubiquitination of ASC in HEK293T cells [48]. Therefore, the inhibition of NLRP3 inflammasomes through molecular inhibitors such as INF58 and MCC950 are most likely to be beneficial in COVID-19 treatment; however, further investigations are required to prove this [48]. Another study has shown that, among five accessory proteins of SARS-CoV tested using a reporter plasmid expressing luciferase (κB-Luc), 3a/X1, and 7a/X4 were capable of activating NF-κB in HEK293T cells [49]. Based on *in vitro* data, the spike protein of SARS CoV induced activation of NF-κB signaling, resulting in IL-6 and TNF-α secretion by murine macrophages [50].

During MERS-CoV infection in Huh-7 and Calu-3 cells, the ORF4b protein binds to karyopherin-α4 (importin-α3), resulting in the inhibition of its interaction with NF-κB-p65 and preventing nuclear translocation

of NF-κB. Accordingly, the expression of pro-inflammatory cytokines, as well as NF-κB-dependent cytokines, increases as a result of the latter event (Fig. 3) [44].

Recently, it was reported that SARS-CoV-2 nsp13 can interact with several transducin-like enhancer (TLE) family proteins regulating the inflammatory response of NF-κB. Physiological evidence shows that TLE 1 is a central negative regulator of inflammation. Also, ORF9c can moderate IκB kinase activity and the NF-κB signaling pathway via the interaction with NDFIP2, NLRX1, F2RL1 [51].

Transforming growth factor β (TGF-β)

TGF-β1 is a type of cytokine that binds to the TGFbRI and TGFbRII serine-threonine kinase receptors through the TGF-β signaling pathway, resulting in the activation of the SMAD-dependent and SMAD-independent pathways [52]. TGF-β1 is a moderator that is capable of enhancing Fas-mediated cell apoptosis, and it also can be the cause of thrombocytopenia and lymphopenia in SARS patients. Generally, viral pathogens such as coronaviruses can target TGF-β signaling in several types of cells [53].

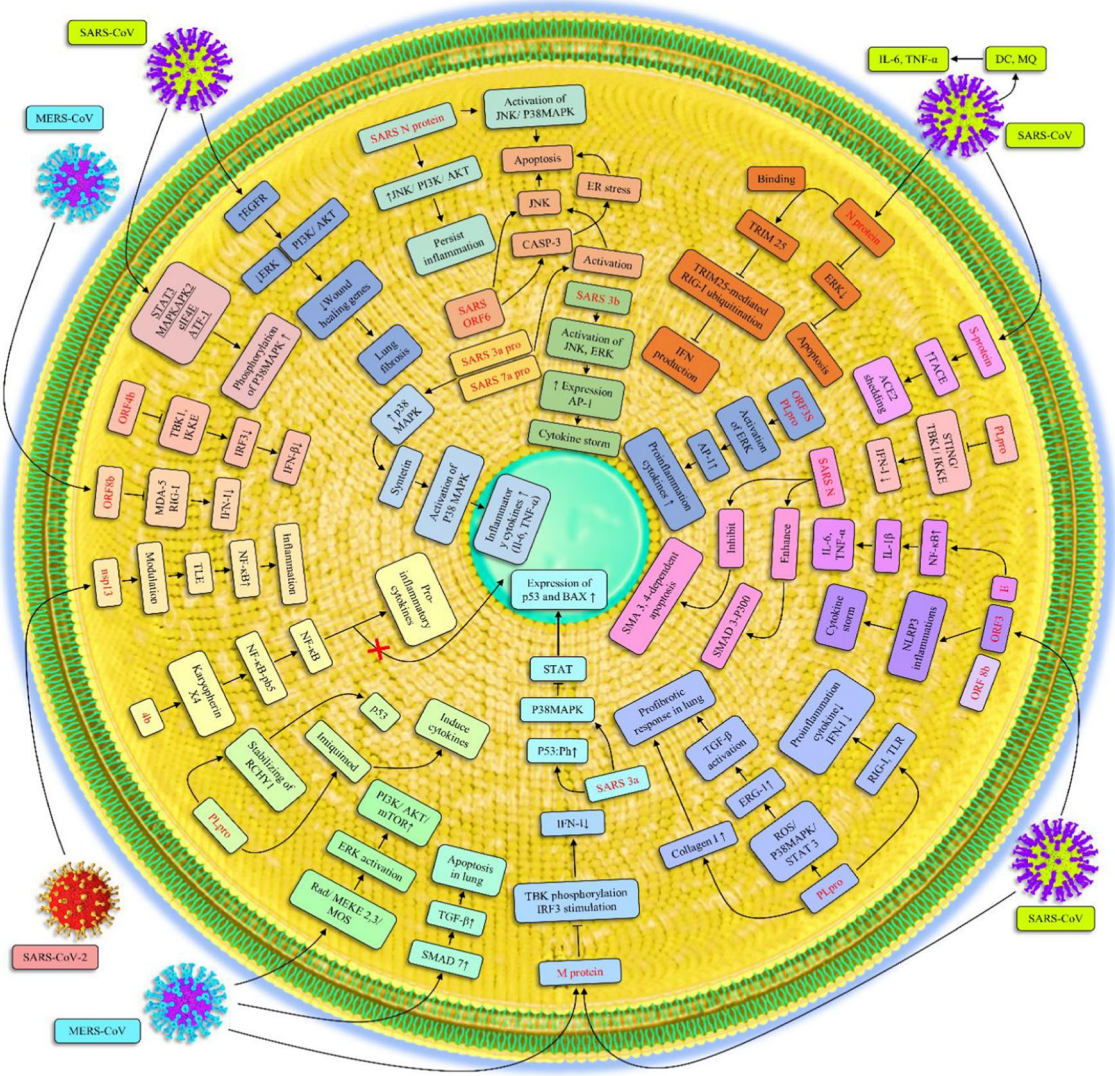

Fig. 3 Cellular signaling pathways that are altered upon coronavirus infection. Once a coronavirus infects its host cell, several cellular signaling pathways are recruited to facilitate the replication of the virus. Despite this recruitment, the activation of such signaling pathways induces inflammation in the host. Most of these signaling pathways, such as EGFR, PI3K/AKT, JNK, can be overactivated by coronavirus proteins, which are mostly affected by the N protein. The viral proteins might also have an impact on P38 MAPK signaling and dysregulate the expression of BAX and BCL2, which are important proteins involved in the apoptosis process. The essential signaling pathway that is mainly inactivated by viral proteins is IFN signaling, and this leads to escape from the host immune response.

During SARS-CoV infection, through the ROS/p38 MAPK/STAT3 axis correlating with elevated pro-fibrotic responses, PLpro induces Egr-1-dependent TGF-β1 promoter activation in human lung epithelial cells and in mouse models [54]. Another study has indicated that SARS-CoV PLpro upregulates the expression of type I collagen via SMAD-independent TGF-β1 signaling, leading to a pro-fibrotic responses in human lung epithelial cells and mouse pulmonary tissues [55]. The SARS-CoV N protein promotes the formation of the SMAD3-p300 complex; however, it can inhibit the activation of SMAD3 and SMAD4-mediated apoptosis in human peripheral lung epithelial HPL1 cells. These results reveal an interesting effect of the N protein of SARS-CoV: inhibiting apoptosis in host cells and promoting tissue fibrosis. They also suggest novel strategies for the treatment of SARS by targeting TGF-signaling compartments [56]. MERS-CoV, like other lethal human coronaviruses, can induce renal and lung cell apoptosis through the upregulation of SMAD7, an important protein in the TGF-β signaling pathway *in vivo* and *in vitro* (Fig. 3) [57]. Given the similarities between of SARS-CoV-2 and SARS-CoV, it could be predicted that the causative agent of COVID-19 also affects the TGF-β signaling pathway in humans.

Cytokine regulation

Macrophages play critical roles in the immune system through cytokine regulation pathways and phagocytosis in response to coronaviruses infection. These innate immune cells are the main sources of cytokines [58]. An immunological and serological study of SARS patients showed that they had a low level of antiviral cytokines (IL-12p40 and IFN-α/β/ γ) and an increased level of pro-inflammatory cytokines (IL-6 and TNF-α) and inflammatory chemokines such as macrophage inflammatory protein 1α (MIP-1α). In addition to the extreme upregulation of inflammatory chemokine, the insufficiency of antiviral cytokines may represent a mechanism by which SARS-CoV escapes from immune responses [59]. A systematic analysis of autopsy specimens from SARS patients demonstrated that the expression of pro-inflammatory cytokines, including TNF-α, monocyte chemoattractant protein-1 (MCP-1), TGF-β1, IL-6, and IL-1β could induce the proliferation of $ACE2^{+}$ cells, which are infected by SARS-CoV- [53]. Exposure to COVID-19 results in higher activated lymphocyte counts and minor monocyte counts than are observed in influenza patients, and in COVID-19 patients, IL-6 and IL-8 levels are increased. IL-6 upregulation in COVID-19 and influenza patients triggers acute respiratory failure. In contrast, granulocyte-macrophage colony-stimulating factor (GM-CSF), IFN-γ, and IL-9 levels are decreased [60]. IL-6 directly or indirectly stimulates glucocorticoid (GC) production, and very high levels indicate COVID-19 immune dysregulation and disease progression [61].

In addition, SARS-CoV PLpro can inhibit the production of type I interferons and pro-inflammatory cytokines through the Toll-like receptor (TLR) and retinoic-acid inducible gene I (RIG-I) pathways. This viral protein has been shown to impede the production of imiquimod-induced cytokine utilizing the suppression of NF-κB activator protein 1 (AP-1) and interferon regulatory factor 3 (IRF-3) *in vitro* [62]. As discussed above, NF-κB can be translocated to the nucleus, leading to increased pro-inflammatory cytokine expression [44]. It has been reported that SARS-CoV ORF8b might also play a critical role in inflammasome activation and cytokine storm and that it triggers NLRP3 activation as well as the release of IL-1β *in vitro* [63]. In a SARS-CoV murine model, IP-10, MIG, and its receptor were upregulated in the lungs, implicating the CXCR3 cascade in the development of ARDS in SARS CoV infection [64].

Increased expression of inflammatory cytokines and chemokines such CXCR3, IL-8 (CXCL8), SOCS5, IL-1β, CCR2, and IL-1α confirms the lung immunopathology in the lower respiratory tracts of patients infected with MERS-CoV. This, along with a decreased Th1 and Th2 response probably leads to severe infection, an increased risk of death, immunopathology, and lung inflammation (Fig. 3) [65]. Moreover, clinical findings have shown that increased levels of IP-10 are also associated with disease progression and poor prognosis in cases of MERS-CoV infection [66].

The modification of upstream cytokine regulation pathways might be a successful strategy for COVID-19 treatment. It has been suggested that more attention should be paid to the dysregulated production of IFN-I in COVID-19 patients, and ALK, cGAS, and STING should be considered potential targets for treatment against a cytokine storm, which occasionally occurs in acute cases of SARS-CoV-2 and SARS-CoV [67]. Increased levels of Th17 CD4 T cells seen in COVID-19 patients can be explained by high levels of IL-6, which is involved in T helper 17 (TH17) cell development [68].

Based on *in vitro* data, there is a significant distinguishable pattern in the cytokine storm seen in COVID-19 that resembles that observed in SARS-CoV and MERS-CoV infection. Only three cytokines, IL-6, IP-10, and IFN-γ, show markedly elevated levels in all three of these highly pathogenic HCoV infections [69]. Lianhuaqingwen (LH), a traditional Chinese medicine, significantly inhibits SARS-CoV-2 proliferation in Vero E6 cells and significantly reduces the production of proinflammatory cytokines, including TNF-α, IL-6, CCL-2/MCP-1, and CXCL-10/IP-10 [70]. In SARS-CoV-2-infected individuals, the proinflammatory cytokines IL-6, IL-10, and TNF-α increase during the disease and decrease during recovery. In addition, IL-6, IL-10, and TNF-α levels are inversely related to CD4 and

CD8 T cell counts. [71]. Previous studies on animals showed that the cytokine storm plays an important role in reducing the adaptive immune response to SARS-CoV infection [72].

p53

One of the critical regulators of the cell cycle that is activated in response to different types of stress through phosphorylation and other post-translational modifications such as acetylation is transcription factor p53 [73, 74]. The upregulation of p53 increases the expression of genes involved in DNA repair (Gadd45α, P53r2, Ddb2, Mgmt), apoptosis (Bax, Noxa, Puma, Pig3), and cell-cycle arrest (14-3-3σ, p21, Btg2, Reprimo) when the damage becomes irreversible [74, 75]. Also, the level of p53 protein in the cell is controlled by the factors MDM2 and MDMX, which together reduce intracellular p53 levels by activating E3 ubiquitin ligase, ultimately leading to degradation of p53 by the proteasome [76, 77]. p53 acts as a tumor suppressor in cancer cells, but recent reports have suggested that p53 can also be involved in antiviral cellular immune responses, assisting in eliminating pathogens such as viruses [78]. Therefore, as a type of cellular stress, viral infections can stimulate the activation of p53, which eventually can induce apoptosis and suppress viral replication [79–81]. Extensive studies have shown that p53 is expressed in response to viral infections that enhance the expression of interferon-stimulated genes (ISG15) and genes encoding interferon regulatory factors (IRF9/5/7) and Toll-like receptor 3 (TLR3), which are involved in the IFN-I-dependent antiviral response [78, 80, 82]. Several studies have revealed that p53 can have both positive and negative effects on various viral infections. Recent observations indicated that p53-dependent apoptosis is detrimental in the early stages of replication of some viruses, but in the late stages of replication, some viruses use apoptosis to transmit completely formed viral particles to other, healthy cells [83]. Previous studies have shown that respiratory viruses, including respiratory syncytial virus (RSV) and influenza virus, cause p53-dependent apoptosis [84, 85].

Also, the murine coronavirus mouse hepatitis virus (MHV) induces cell cycle arrest by activating transcription factor p53, which favors viral infection [86]. Previous studies have also illustrated that the SARS-CoV 3a protein leads to cell cycle arrest by increasing phosphorylation of p53 in HEK 293 cells [87].

Yuan *et al.,* based on *in vitro* and *in vivo* data, demonstrated that PLpro of HCoV-NL63 inhibits the p53-dependent antiviral response by reducing the stability of the p53 transcription factor via increasing MDM2-mediated ubiquitination, which ultimately leads to enhanced virus replication [88]. Furthermore, Ma-Lauer *et al.* revealed that in coronaviruses such as MERS-CoV and SARS-CoV, p53 acts as a negative regulator and reduces virus replication. These researchers proposed that nsp3 has the protective SARS-unique domain (SUD) and PLpro, which counteract the antiviral effect of p53. The *in vitro* and *in vivo* data indicate that SUD and PLpro together destroy p53 and inhibit the host cell's defense response by stabilizing E3 ubiquitin ligase RCHY1 [89]. Moreover, the 3a protein of SARS-CoV increases apoptosis in host cells by indirect activation of p53. The 3a protein increases the expression level of p53 and Bax by increasing the activity of the p38 MAPK signaling pathway and inhibiting the STAT signaling pathway, which directly inhibits p53 *in vitro* [90]. Recent clinical studies have shown that SARS-CoV-2 infection can cause apoptosis of lymphocytes. Interestingly, in patients with lymphopenia, p53, an important factor associated with apoptosis, is significantly increased [91]. Compared to other coronaviruses such as MERS-CoV and SARS-CoV, it has been shown that SARS-CoV-2 is more sensitive to the IFN-I-dependent antiviral response in the early stages of infection [92]. Since p53 plays a critical role in inducing this response, it is destroyed by MERS-CoV and SARS-CoV. SARS-CoV-2 might also inhibit antiviral responses by destroying p53. Moreover, since MERS-CoV and SARS-CoV use p53 signaling to induce apoptosis and cell cycle arrest, SARS-CoV-2 might also use the p53 pathway to induce cell cycle arrest and apoptosis (Fig. 3).

EGFR

EGFR belongs to the family of receptor tyrosine kinases (RTKs). These are transmembrane proteins with an extracellular domain for ligand binding and an intracellular domain. They regulate many cellular processes by activating downstream signaling pathways such as the PI3K/AKT, Ras/Raf/MAPK, STAT, and Src kinase pathways via phosphorylation [93]. Upregulation of this pathway has been seen in many cancers that increase cell migration and proliferation. The over-activation of EGFR upon a viral infection has a major role in the entry of the virus into the host cell, producing more mucus and activating the inflammatory response [94, 95]. Recent reports have suggested that EGFR signaling stimulates the uptake of influenza A virus (IAV) and transmissible gastroenteritis virus (TGEV) into the host cell [96, 97]. In addition, other studies have shown that respiratory viral infections and PEV infections suppress the antiviral response by increasing the activity of the EGFR signaling pathway [98, 99]. Studies have also indicated that CoV-induced macropinocytosis is reliant on the activation of EGFR, which stimulates macropinocytosis pathways within the cell. SARS-CoV and MHV infections stimulate macropinocytosis, which occurs during late infection *in vitro* [100].

Extensive studies have shown that the EGFR signaling pathway plays a critical role in the progression of lung

fibrosis. The role of EGFR in fibrosis progression has been investigated using *in vivo* models, primarily mice [101]. Using mouse models of SARS-CoV pathogenesis, it has been shown that the wound repair pathway, controlled by EGFR, is critical for recovery from SARS-CoV-induced tissue damage. SARS-CoV infection in the early stages causes acute lung injury, and in the middle stages, the symptoms of fibrosis appear in the lungs. Many survivors of SARS-CoV infection have a high risk of developing pulmonary fibrosis. EGFR signaling is an important regulator of SARS-CoV-induced lung damage. Hence, researchers have suggested that the upregulation of the EGFR pathway after SARS-CoV infection increases fibrosis. Therefore, the use of tyrosine kinase inhibitors such as erlotinib and related compounds is able to reverse or inhibit fibrosis development in a variety of animal models [102]. Activation of EGFR regulates downstream signaling pathways such as AKT, PI3K, and ERK, which are involved in inducing expression of wound-healing genes. It has also been seen that fibrosis caused by SARS-CoV is independent of the role of various types of interferon. Therefore, inhibition of EGFR could avert an excessive fibrotic response to SARS-CoV (Fig. 3) [102, 103]. SARS-CoV-2, like other emerging respiratory viruses, may induce pulmonary fibrosis in survivors of SARS-CoV-2 infection by activating the EGFR pathway. SARS-CoV-2 leads to pulmonary injury, and EGFR might facilitate its entry to the host cell and cause an inflammatory responses. Therefore, understanding how EGFR functions after a viral infection may lead to new treatments in the future.

JNK

C-Jun NH2-terminal kinase (JNK1/JNK2) signaling is an MAPK downstream pathway activated through phosphorylation by MKK7 and MKK4, which ultimately leads to numerous cellular processes, such as the inflammatory response, cell proliferation, survival, and death. The JNK signaling cascade is activated in response to various types of cellular stress, pathogens, and growth factors. One of the main targets of the JNK signaling pathway, which is involved in the pathogenicity of viruses by activating antiviral and pro-inflammatory cytokines, is the transcription factor activator protein 1 (AP-1) [104, 105]. Research shows that JNKs are important kinases that are activated in innate immune responses to viral infection and stimulate the activity of several significant cytokines, such as interleukins (IL-2, IL-4) and interferon gamma (IFN-γ) [106]. Recent reports have indicated that RSV and influenza A virus (IAV) increase the activity of the JNK/AP-1 signaling pathway [107, 108].

The coronavirus infectious bronchitis virus (IBV) stimulates the activity of the JNK signaling pathway by activating MKK7, which ultimately increases virus-induced apoptosis in H1299 cells. Paradoxically, inhibition of the JNK signaling pathway by SP600125 eliminates the inhibitory effect of JNK on the anti-apoptotic protein Bcl2 in Huh-7 cells, which ultimately reduces apoptosis during IBV infection [109]. Also, when Vero cells were transfected with a Bcl-2 expression plasmid and then infected with SARS-CoV, **??**overexpression**??** of Bcl-2 or other anti-apoptotic proteins protected cells against coronavirus-induced apoptosis [110, 111]. Another study found that the JNK signaling pathway is activated during HCoV-229E infection and plays an anti-apoptotic role through the modulation of Bcl2 family proteins. Activation of JNK also regulates innate immunity by inducing IFN-β and IL-8 [112]. Moreover, the JNK signaling pathway plays a crucial role in SARS-CoV infection [109]. Hence, the phosphorylation of JNK and its upstream pathways have been observed during this viral infection. JNK and PI3K/AKT signaling pathways could be phosphorylated by the N protein of SARS-CoV, causing the establishment of persistent SARS-CoV infection in Vero E6 cells [113, 114]. Moreover, the N protein of SARS-CoV is involved in the induction of apoptosis through the JNK activation and p38 MAPK signaling pathways in the absence of growth factors in COS-1 monkey kidney cells [115]. Also, Ye *et al.* observed that the protein encoded by ORF6 of SARS-CoV induces apoptosis by caspase-3-mediated ER stress and JNK-dependent signaling pathways in Vero E6 cells [116]. Upregulation of SARS-CoV 3a and 7a protein has also been demonstrated to induce JNK activation in HEK293T cells [49]. Furthermore, the SARS-CoV 3b protein stimulates the expression of the transcription factor AP-1 by activating JNK and ERK signaling pathways in Huh7 cells. Activation of AP-1 by the 3b protein stimulates the pro-inflammatory cytokines that are involved in cytokine storm production in SARS-CoV infection (Fig. 3) [117]. As with SARS-CoV, JNK and its upstream signaling pathways, such as MKK4 and MKK7, might play a major role in SARS-CoV-2-induced apoptosis. SARS-CoV-2, like SARS-CoV may induce the production of pro-inflammatory cytokines through AP-1 activation in response to the infection.

p38 MAPK

The p38 MAPK family comprises four groups of 38-kDa protein (p38) [118]. It is activated by phosphorylation at the sequence Thr180-Gly181-Tyr182, called the activation loop, when exposed to growth factors, environmental stresses such as viral infections, and inflammatory cytokines [118, 119]. The p38 MAPK signaling pathway plays various roles depending on the type of stimulation and also the type of tissue exposed to such stimulus. Hence, p38 MAPK signaling can increase both cell death and survival [120, 121]. Its key role has been observed in many viral infections that cause respiratory symptoms; in HCoV-229E, the activation of p38 MAPK is needed to induce CPE (cytopathic effect)

and viral replication [122]. Mouse hepatitis virus (MHV, also known as murine coronavirus) requires p38 MAPK activation for its replication, and its activation leads to the phosphorylation of eIF4E to translate host proteins, such as IL-6 to synthesize a virus-specific protein [123]. Also, influenza A virus (H5N1) activates p38 MAPK to induce cytokines [124]. Avian infectious bronchitis virus (IBV) induces IL-6 and IL-8 production via phosphorylation of p38 MAPK, while dual-specificity phosphatase 1 (DUSP1), a protein phosphatase, in cells infected with IBV, is upregulated to dephosphorylate p38 MAPK in order to regulate pro-inflammatory cytokine [125].

In SARS-CoV-infected cells, at the *in vitro* stage, p38 MAPK is phosphorylated through downstream effectors such as STAT3, MAPK-activated protein kinase 2 (MAPKAPK2), eIF4E (eukaryotic translation initiation factor 4E) and activating transcription factor 1 (ATF-1) [126–128]. SARS-CoV-infected Vero E6 cells exhibit an elevated level of phosphorylated p38 MAPK [128]. Moreover, the 3a protein of SARS-CoV increases the p53 level, leading to p38 MAPK activation and the upregulation of *Bax* expression, which consequently triggers the intrinsic apoptosis pathway *in vitro* [90]. *In vitro* data have indicated that SARS-CoV induces apoptosis to cause intense damage in lung tissue, which is one of the prominent symptoms of this disease [129]. Besides the 3a protein, the 7a protein not only activates apoptosis by activating p38 MAPK but also inhibits translation *in vitro* [130]. Moreover, the N protein of SARS-CoV in COS-1 monkey kidney cells stimulates apoptosis via p38 MAPK upregulation [115]. In SARS-CoV, TGF-β1 is upregulated through the Egr-1-mediated pathway, which is induced by the papain-like protease (PLpro). TGF-β1 prompts lung fibrosis both in mouse and human lung tissues through the ROS/p38 MAPK/STAT3 pathway, triggered by SARS-CoV PLpro [54]. During SARS-CoV infection, syntenin activates p38 MAPK to increase inflammatory cytokines [131]. Cells infected with recombinant SARS-CoV lacking the envelope protein (E) PDZ-binding motif (PBM, a domain involved in protein-protein interactions) have lower levels of p38 MAPK, suggesting that E protein is involved in the severity of the infection *in vivo* [131]. An increased level of phosphorylated p38 MAPK in SARS patients results in high levels of IL-8 and aberrant cytokine levels [132]. Moreover, an *in vitro* experiment showed that the p38 MAPK inhibitor had an antiviral effect against MERS-CoV (Fig. 3) [133]. SARS-CoV-2 proteins may directly stimulate p38 activity to promote replication. The upregulation of p38 MAPK may also facilitate viral entry by ACE2 endocytosis and cause inflammation, thrombosis, and vasoconstriction in COVID-19 patients [134].

As mentioned above, SARS-CoV proteins such as 3a, 7a, N, and E are involved in activating p38 MAPK, suggesting that SARS-CoV-2 proteins may also be involved in triggering the p38 MAPK signaling pathway. One of the well-known symptoms of coronavirus infection is pulmonary injury. In SARS-CoV cases, the p38 MAPK pathway, via p53, TGF-β1, and syntenin, leads to apoptosis via interaction with different molecules, resulting in lung injury. SARS-CoV-2 is therefore likely to use p38 MAPK signaling to induce apoptosis and lung damage.

Extracellular signal-regulated kinase (ERK)

ERK is one of the main members of the MAPK signaling pathways [135]. ERK1 and ERK2, also referred to p44/42 MAPK, are involved in cell proliferation, survival, motility, and differentiation when exposed to mitogens and extracellular stimulants [136, 137]. Activation of the ERK pathway depends on binding of Ras to the cell membrane to initiate the cascade, after which ERK is phosphorylated at the sequence Thr183-Glu184-Tyr185 and is then translocated to the nucleus [138–140].

It has been shown that ERK1/2 and MEK1/2 knockdown prevents the replication of the murine coronavirus genome but does not affect protein translation or virus entry [141]. Endothelin 1 (ET-1) is upregulated in pulmonary fibrosis, induces the MEK/ERK MAP kinase pathway, and increases CCN2 mRNA and protein levels [142]. In idiopathic pulmonary fibrosis (IPF), TGFβ-1, through the ERK1/2 pathway, stimulates the transformation of human lung fibroblasts into myofibroblasts [143, 144]. It also increases α-SMA and collagen expression in the lung by activating ERK1/2 and inhibiting GSK-3 and β-catenin translocation to the nucleus [145]. Activation of the ERK signaling pathway has been observed during infections with respiratory viruses, including influenza virus (SIV, H1N1pdm), avian H9N2 influenza virus, and RSV [146, 147]. This suggests the participation of the ERK signaling pathway during respiratory virus infection. It has been demonstrated that coronaviruses can also recruit this pathway to facilitate their replication and pathogenesis.

Both p38 MAPK and ERK1/2 are phosphorylated and activated in Vero E6 cells infected with SARS-CoV [128]. P90RSK, a downstream element of ERK, is phosphorylated at Ser380 by p38 MAPK and plays a major role in SARS-CoV-infected cells when its Thr573 phosphorylation is decreased [148]. p90RSK controls apoptosis, which has been shown by treatment of SARS-CoV-infected Vero E6 cells with PD98059 (an ERK inhibitor) and SB203580 (a p38 inhibitor), which reduced p90RSK phosphorylation. However, the ERK inhibitor did not prevent major damage to the infected cell [148]. Thus, ERK phosphorylation is not sufficient to prevent apoptosis induced by SARS-CoV infection due to Akt activation [149].

Surjit *et al*. demonstrated that the SARS-CoV N protein induces apoptosis in COS-1 cells via downregulation of ERK in cells that are free from growth factors [115]. AP-1

controls cytokine transcription due to SARS-CoV infection, and ERK activation upregulates AP-1 activity via c-Fos *in vitro* [117]. In addition, 3b, one of the accessory proteins of SARS-CoV [150], stimulates AP-1-related genes [117]. ORF3b induces AP-1 transcriptional activity by activating ERK pathways [117]. SARS-CoV, via the S, PLpro, 3b proteins, and MERS-CoV, via Raf/MEKK2,3/Mos and then MKK1,2,5, induces ERK signaling [112]. Furthermore, the ERK/MAPK pathway, along with the PI3K/AKT/mTOR pathway, plays a crucial role in the pathogenesis of MERS-CoV, and inhibition of this pathway prevents MERS-CoV proliferation *in vitro* [151]. Taken together, the ERK signaling pathway is essential for pathogenicity, preventing host cell apoptosis and causing lung injury and viral spread. COVID-19 leads to the release of pro-inflammatory cytokines such as IL-1β and IL-6 to provoke lung inflammation, fever, and fibrosis [152]. As mentioned above, ERK stimulates AP-1 activation through 3b and ORF3b viral proteins to increase cytokine expression and via the N protein to increase survival of host cells infected with SARS-CoV (Fig. 3). It is therefore likely that ERK could activate AP-1 and cytokine expression in SARS-CoV-2 infection.

TNF-α

TNF-α belongs to the TNF superfamily of transmembrane proteins and is a proinflammatory cytokine that is mainly secreted from macrophages [153]. Its essential roles in defense against pathogens are immunoregulation and inhibition of infection factors and tumor formation [154, 155], and it is associated with many diseases [156]. This cytokine mediates the inflammatory response and is important for the host cell defense against pathogens. Excessive expression of TNF-α can exacerbate disease [156]. Each person has a different ability to produce cytokines that is related to that individual's genetic background [157]. TNF-α is associated with autoimmune diseases, such as rheumatoid arthritis, inflammatory bowel disease, psoriasis, and refractory asthma [158]. It has various effects. For instance, it increases the release of pro-inflammatory factors, enhances the production of adhesion molecules, and increases migration of eosinophils and neutrophils. Moreover, its levels are elevated in mice infected with human adenovirus B1[159] and in humans infected with H1N1 influenza virus [160]. The capsid of hepatitis B virus strongly induces TNF-α production in human THP-1 macrophages [161]. Activation of Toll-like receptor 2 (TLR2) by binding to viruses such as hepatitis C virus (HCV) [162], measles virus [163], and various herpesviruses, including herpes simplex virus (HSV) [164] and cytomegalovirus [165], is followed by TNF-α production. TNF-α is associated with lung fibrosis [166] and pulmonary fibrosis [167], which, together with IL-1, is overexpressed in regenerating type 2 pneumocytes in the lung [166]. In IPF progression, epithelial cells release cytokines such as TNF-α, which induce the transformation of fibroblasts into myofibroblasts and the production of extracellular matrix molecules, leading to respiratory insufficiency [168].

In SARS patients, analysis of serum cytokine levels has shown large amounts of TNF-α, which suggests that TNF-α is involved in SARS pathogenesis [169] by causing excessive inflammation [170]. The TNF-α level is significantly increased in the acute stage and reduced in the convalescent stage of illness in SARS patients [171], suggesting that TNF-α plays a pivotal role in the pulmonary injury triggered by SARS coronavirus, and TNF-α inhibitors can be a potent factor in treatment of acute respiratory disease syndrome caused by coronavirus infection [172]. The SARS-CoV S protein attaches to the host cell receptor to initiate infection [33]. The S protein induces IL-6 and TNF-α production via the NF-κB pathway activation in RAW264.7 cells, which are murine macrophages [50]. Moreover, p38 MAPK activation gives rise to TNF-α and IL-6 production [173, 174]. It is thought that incubation of RAW264.7 cells with the S protein activates the p38 pathway, thus increasing TNF-α and IL-6 levels [50]. Additionally, SARS-CoV infection induces TNF-α and IL-6 production in dendritic cells and human macrophages [59, 175]. Haga *et al.*, demonstrated *in vitro* that SARS-CoV S prompts TNF-α converting enzyme (TACE, also called ADAM17) to cause ACE-2 ectodomain shedding, which is followed by the production of TNF-α, facilitating viral entry and increasing tissue injury [176]. TACE continuously sheds ACE-2 in the epithelium of the human airway to release soluble ACE2 (sACE2), which is active [177]. There is no evidence that TNF-α obstruction is dangerous for COVID-19 patients [158]. TNF-α is present at high levels in immune response cells, such as dendritic cells and macrophages in the case of SARS-CoV infection. TNF-α also intensifies the harmful effects of SARS-CoV infection, such as lung tissue injury, and facilitates virus entry (Fig. 3). SARS-CoV-2 is known to cause severe pulmonary damage, which is consistent with the theory that TNF-α worsens the symptoms of SARS-CoV-2 infection and promotes overproduction of cytokines via the S protein and that TACE may also be involved in the entry of SARS-CoV-2.

Interferon signaling pathway

The innate immune response is the first step in protection against pathogens [178]. In viral infections, it stimulates the interferon signaling pathway and, ultimately, the expression of IFN-I, which leads to an antiviral response in cells [179]. IFN-I binds to cell-surface co-receptors and stimulates the Janus kinase (JAK) signal transducer and STAT signaling network, which upregulates several IFN-stimulated genes (ISGs). Numerous proteins encoded by these ISGs are

responsible for antiviral functions [180]. However, viruses have developed various mechanisms to interfere with IFN expression, and this appears to apply to coronaviruses. In SARS-CoV, MERS-CoV, and other CoVs, the response to viral infection through IFN-I is hampered. These CoVs use different mechanisms to reduce the production of IFN-I. This suppression strategy is closely correlated with disease severity and mortality [181].

TGEV, a member of the genus *Alphacoronavirus*, escapes the effect of IFN-I through IRE1α-based manipulation of the miR-30a-5p/SOCS1/3 axis. Recent studies have indicated that the interaction between the C-terminus of the SARS-CoV (and also MERS-CoV) N protein and the SPRY domain of tripartite motif protein 25 (TRIM25) prevents TRIM25-mediated RIG-I ubiquitination, leading to the suppression of IFN production *in vitro* [182, 183]. Lui *et al.* have proposed a strategy through which MERS-CoV and SARS-CoV utilize their M proteins to inhibit IFN-I expression at the level of TANK-binding kinase 1 (TBK1)-associated phosphorylation and stimulation of interferon regulatory factor 3 (IRF3), leading to evasion of the innate antiviral response in HEK-293 cells [184]. A recent study revealed that the SARS-CoV proteins 8ab and 8b are IFN antagonists. This *in vitro* study demonstrated the direct association of these two proteins with IRF3. It was also found that they moderately inhibit IFN stimulation by restricting IRF3 activation and by increasing the proteasome-dependent destruction of IRF3 [185]. Moreover, of the SARS-CoV viral proteins, ORF3b, M, ORF6, N, PLP, nsp1, nsp7, and nsp15 have been identified as interferon antagonists [186–188]. Lee *et al.* have reported that ORF8b of MERS-CoV is an effective antagonist of both MDA5 (melanoma differentiation-associated protein 5)- and RIG-I (retinoic acid-inducible gene I)-mediated stimulation of IFN signaling *in vitro* [189].

In vitro data have shown that the expression of the membrane-anchored PLpro domain (PLpro-TM) of SARS-CoV prevents STING/TBK1/IKKε-based stimulation of IFN-I and disrupts the phosphorylation and dimerization of IRF3, which are triggered via STING (stimulator of interferon genes) and TBK1. Additionally, PLpro-TM physically interacts with TRAF3, TBK1, IκB kinase ε (IKKε), STING, and IRF3, the significant factors that form the STING-TRAF3-TBK1 complex for stimulation of IFN expression [190]. Yang and colleagues have proposed a model of the IFN antagonism strategy of MERS-CoV ORF4b in HeLa and 293T cells in which ORF4b binding to TBK1 and IKKε stops the molecular interplay between mitochondrial antiviral signaling protein (MAVS) and IKKε and prevents IRF3 phosphorylation and stimulation of IFN-β production (Fig. 3) [191]. Despite the well-known effects of IFN-I as an antiviral and immunomodulatory factor that contributes to protection against viral infections, it has become clear that IFN-I also supports adverse inflammatory responses in several bacterial, fungal, and chronic virus infections. Using BALB/c mice infected with SARS-CoV, Channappanavar et al. revealed that rapid virus replication and delayed IFN-I signaling results in inflammatory responses and lung immunopathology that threaten survival. This delayed IFN-I signaling stimulates the accumulation of inflammatory monocyte-macrophages, leading to increased cytokine/chemokine levels in the lung, vascular leakage, and reduced virus-specific T cell responses [72]. Thus, dysregulated IFN-I and inflammation pathways converge to cause lung damage in a SARS-CoV model. By screening the SARS-CoV-2 viral proteins, researchers have found that the viral proteins ORF6, ORF8, and nucleocapsid are potent inhibitors of the interferon type I signaling pathway. These proteins have been shown to inhibit interferon-stimulated genes (ISGs) such as ISG54 and ISG56 in HEK-293 T cells [192]. Moreover, by screening 23 viral proteins, it has been shown that the SARS-CoV-2 nsp, nsp3, nsp12, nsp13, nsp14, ORF3, ORF6, and M proteins inhibit Sendai-virus-induced IFN-β promoter activation [193]. Also, Xia *et al.* have shown that SARS-CoV-2 proteins suppress the IFN-I response *in vitro*. They found that nsp6, nsp13, and ORF6 suppress phosphorylation of TBK1 and IRF3, which is essential for the induction of the IFN-β pathway. Compared with SARS-CoV and MERS-CoV, IFN-I signaling is more efficiently inhibited by nsp1 and nsp6 of SARS-CoV-2 [194]. Mantlo *et al*. assessed the sensitivity of SARS-CoV-2 to both IFN-α and IFN-β *in vitro*. They found that IFN-I has potent anti-SARS-CoV-2 activity in cultured cells – a finding that could inform future treatment options for COVID-19 [195]. The progress of disease and viral transmission depend on immune antagonism and the level of viral replication. Using *ex vivo* human lung tissue explants, it has been shown that SARS-CoV-2 infection of lung tissues, despite producing a large amount of virus, induces a relatively small amount of IFN and pro-inflammatory cytokines/chemokines in comparison to SARS-CoV infection, which might explain why the virus is transmitted by individuals without symptoms and with delayed onset of COVID-19 disease [70]. The rapid appearance of SARS-CoV-2 has prompted increased investigation of innate immune responses to CoVs. Recent research has shown that SARS-CoV-2 stimulates insignificant expression of IFNs (type I, II, or III) in infected cells, even when compared to other coronaviruses. This lack of IFN production probably weakens the primary innate immune response to SARS-CoV-2 infection and suggests that exogenous IFN treatment can be successful against SARS-CoV-2 [196]. Most COVID-19 patients with acute respiratory failure, instead of a cytokine storm, have IFN-I and -II immunosuppression. The IFN-γ and IFN-α response pathways are seriously depressed in B

cells, $CD8^+$ T cells, **??**mixed cytolytic lymphocyte populations**??** (MCLPs), Tregs, **??**plasmacytoid dendritic cells**??**, and monocyte/macrophage subsets of COVID-19-infected subjects [197].

Lokugamage *et al.* have shown that SARS-CoV-2 is much more sensitive to IFN-I than SARS-CoV is in Vero and in Calu3 cells. This increased sensitivity to IFN-I is probably due to differences in the viral proteins of these two CoVs [198]. Different studies have shown that SARS-CoV-2 nsp13 (helicase), nsp14 (exonuclease), nsp15 (endoribonuclease), and accessory protein ORF6 are the strongest viral interferon antagonists [193, 199]. Unlike other respiratory viruses, the IFN-I and IFN-III levels are reduced in SARS-CoV-2 infections, and it should be noted that increasing IFN leads to a significant reduction in virus replication, and even SARS-CoV is limited by IFN-α [200]. Moreover, high levels of circulating neutrophils caused by the induction of CXCL2 and CXCL8 contribute to disease severity in COVID-19 patients [201].

We therefore conclude that antagonism of IFN by SARS-CoV-2 and the ability to block other pathways of innate antiviral signaling might determine the severity of the disease. This prediction is based on the hypothesis that the immune response against SARS-CoV-2 is similar to that against other CoVs, which needs to be confirmed through future studies on SARS-CoV-2.

PI3K/AKT

The PI3K/AKT pathway controls various cellular processes, such as antiviral immunity, cell proliferation, protein translation, RNA processing, apoptosis, and autophagy [202]. Several host cellular signaling pathways are stimulated and exploited by viruses to allow successful cycles of replication. The PI3K/AKT pathway has recently received significant attention because of its function in controlling virus replication. This pathway has been shown to be essential not only for viral cell entry but also for subsequent intracellular trafficking and replication of some viruses [203]. Apoptosis functions as an operative antiviral mechanism in an infected organism that is simple and usually successful. Thus, to protect its replication, the virus must inhibit or postpone apoptosis. One of the mechanisms used by viruses to prolong viral replication and slow down apoptosis in both persistent and acute infections is altering PI3K/AKT signaling [204]. PI3K/AKT signaling is also involved in upregulating the interferon response, and increasing PI3K/AKT activity can stop viral spread due to the initiation of cellular defenses [205]. Stimulation of this pathway by influenza virus decreases IRF-3-based promoter functions and dimerization of IRF-3, resulting in a reduction in host antiviral activity [206]. Kindrachuk *et al.* demonstrated that *in vitro* MERS-CoV replication could be substantially inhibited by treatment with a group of licensed kinase inhibitors targeting the PI3K/AKT/mTOR pathway. This suggests that PI3K/AKT/mTOR signaling plays a central role in MERS-CoV infection and may indicate new drug targets for treatment [151]. Also, it is found that the PI3K/AKT signaling pathway is vital for the initiation of SARS-CoV infection in Vero E6 cells, and no viable cells were detected after treatment with the PI3K/AKT inhibitor LY294002 [114, 207]. Moreover, Chan *et al*. found that the M protein of SARS-CoV modulates the cellular AKT pro-survival pathway and mitochondrial cytochrome c secretion and stimulates apoptosis in both HEK293T cells and transgenic drosophila (Fig. 3) [208].

Based on information obtained from studies of other CoVs, we consider it likely that infection with SARS-CoV-2 stimulates PI3K/AKT signaling and that preventing P13K activation can lessen the severity of viral infections.

Signaling pathways that are likely to be dysregulated upon infection with SARS-CoV-2

The SARS-CoV-2 global crisis has reminded everyone that viruses are constantly changing genetically and functionally to better infect different species, including humans [209]. Coronaviruses, on the one hand, functionally paralyze their host cells and, on the other hand, force them to produce their essential proteins. In the meantime, many of the host cell's signaling pathways undergo alterations that can worsen the disease condition caused by these viruses. In the current review, we have summarized information about several signaling pathways that are affected by coronavirus infections and illustrated the mechanisms by which this occurs. The main purpose of a virus upon its entry into the host cell is to replicate its RNA/DNA, maintain or over-activate the machinery for protein production in the host cell, and evade immune responses by the host. Considering the ability of coronavirus infections, particularly SARS-CoV-2 infections, to induce inflammation and lung injury and also the similarity of this novel virus to MERS-CoV and SARS-CoV in its ability to infect lung epithelial cells, it is expected that this emerging life-threatening coronavirus utilizes some of the same cellular signaling pathways as MERS-CoV and SARS-CoV. As a therapeutic approach, the use of anti-inflammatory agents during COVID-19 to affect inflammatory signaling pathways might be beneficial for reducing the severity of the disease (Table 1). The NF-κB, cytokine regulation, ERK, and TNF-α signaling pathways have been shown to be likely causes of inflammation in MERS-CoV and SARS-CoV infections, with neutrophilia and basophilia exacerbating the disease in SARS patients [210]. The increased levels of inflammatory cytokines in serum of COVID-19 patients

Table 1 Drugs reported to affect signaling pathways that are altered upon coronavirus infection

Drug	Target	Main use	Use in coronavirus-related disease	Refs
Sorafenib	JNK	Suppresses hepatitis B virus gene expression	Against MERS-CoV and SARS-CoV	[211, 212]
Berberine	JNK	Inhibits coxsackievirus replication	Antiviral activity against SARS-CoV and other coronaviruses, also against SARS-CoV-2	[213–215]
SP600125	JNK	Inhibits human cytomegalovirus replication, anti-cancer	Kills SARS-CoV-infected cells	[113, 216, 217]
AS601245	JNK	Anti-inflammatory, anti-cancer		[218]
Ginsenoside Rg1	JNK	Suppresses liver necrosis and inflammatory responses		[219]
BI-78D3	JNK	Anti-cancer		[220]
BX-795	JNK/p38	Inhibits HSV-1 and HSV-2 replication		[221]
Gefitinib	EGFR	Suppresses respiratory viral infection		[222]
AG148	EGFR	Inhibits cell proliferation and arrests the cell cycle		[223]
Erlotinib	EGFR	Inhibits HBV replication, anti-cancer		[224, 225]
Lapatinib	EGFR	Anti-cancer	As a therapy for COVID-19	[226, 227]
Afatinib	EGFR	Prevents an excessive fibrotic response in SARS-CoV and other respiratory viral infections		[102]
Rociletinib (CO-1686)	EGFR	Anti-cancer		[228]
Pifithrin-α	p53	A chemical inhibitor of p53 that protects mice from the side effects of cancer therapy		[229]
2-Sulfonylpyrimidine (PK11007)	mutant p53	Potential new treatment for triple-negative breast cancer (TNBC)		[230]
ReACp53	mutant p53	Induces mitochondrial cell death and reduces DNA synthesis		[231]
SB 239063	p38 MAPK	Lung fibrosis		[232]
SB202190	p38 MAPK	Renal fibrosis	By inhibiting p38MAPK decreases the cytopathic effects of SARS-CoV infection	[127, 233]
SB203580	p38 MAPK	Hypothalamus inflammation	Effectively inhibits phosphorylation of HSP-27, CREB, and eIF4E in SARS-CoV-infected cells	[128, 234]
BIRB796	p38 MAPK	Cervical cancer		[235]
SB 239063 and SKF 86002	p38 MAPK	Septic lung injury		[236]
FR180204	ERK	Cancer treatment		[237]
ERK5-IN-1	ERK	Regulates MDR potential		[238]
Etanercept, infliximab, adalimumab	TNF-α	Treatment of autoimmune diseases such as rheumatoid arthritis, Crohn's disease, and psoriasis	Reducing coronavirus-related pulmonary injury, against SARS-CoV-2 infection	[239, 240]
Certolizumab and golimumab	TNF-α	Treatment of autoimmune diseases such as rheumatoid arthritis, Crohn's disease, and psoriasis		[239]
Celastrol	TNF-α	represses inflammation and propagation in RAW264.7 cells	Inhibitor of SARS-CoV $3CL^{pro}$, anti-MERS	[241–243]
Triptolide	TNF-α	In the differentiation of osteoblasts	Rescue mitochondrial dysfunction induced by SARS-CoV-2	[244, 245]

Table 1 (continued)

Drug	Target	Main use	Use in coronavirus-related disease	Refs
Bithionol, chromomycin A3, cantharidin, ecteinascidin 743, fluorosalan hydrochloride, narasin, sunitinib malate, tioconazole, tribromsalan, triclabendazole, zafirlukast	NF-κB	Anti-cancer		[246]
Bortezomib (Velcade)	NF-κB	Anti-cancer	Impairs entry and RNA synthesis of different CoVs	[246, 247]
Daunorubicin	NF-κB	Anti-cancer	Potential treatment against SARS-CoV-2 infection	[246, 248]
Digitoxin	NF-κB	Anti-cancer	Therapeutic role against COVID-19 with hypercytokinemia	[246, 249]
Emetine	NF-κB	Anti-cancer	Inhibits SARS-CoV-2 replication	[246, 250]
Manidipine	NF-κB	Anti-cancer	Inhibits SARS-CoV-2 cysteine proteases Mpro (3CLpro)	[246, 251]
Lestaurtinib	NF-κB	Anti-cancer	COVID-19 treatment	[246, 252]
Ouabain	NF-κB	Anti-cancer	COVID-19 treatment	[246, 249]
Sorafenib tosylate	NF-κB	Anti-cancer	Prevents SARS-CoV-2 replication, used against MERS-CoV	[246, 253]
Metformin	TGF-B	For numerous diseases in which TGF-β1 hyperfunction is indicated	Prevents SARS-CoV-2 entry	[254, 255]
Fresolimumab (GC1008): monoclonal antibodies against TGF-β	TGF-B	Anti-cancer		[256]
Lanreotide, romidepsin, pasireotide	TGF-B	Anti-cancer		[257]
Rituximab	PI3K/AKT	Stops the PI3K/AKT pathway in B-NHL cell lines and sensitizes the drug-resistant tumor cells to apoptosis		[258]
Gefitinib	PI3K/AKT	Overcomes acquired drug resistance by regulating the PI3K/AKT pathway in non-small cell lung cancer		[259]
Anlotinib	PI3K/AKT	Overcomes multiple-drug-resistant colorectal cancer cells by inactivating PI3K/AKT pathway		[260]
Sorafenib	IFN signaling	Leads by to the significant down-modulation of IFN-γR1 in renal cell carcinoma		[261]

have shed light on the involvement of such signaling pathways in the pathogenesis infection of SARS-CoV-2. Further studies are needed to clarify the exact roles of cellular signaling pathways once the SARS-CoV-2 initiates infection in its host cell. Also, researchers in molecular medicine should consider the roles of the most strongly up- and downregulated components of cellular signaling pathways during COVID-19 to identify and design better molecular drugs that will decrease the fatality rate of this novel pandemic coronavirus.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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