The alterations of cellular signaling pathways in the host cell upon the high pathogenic Coronaviruses infection, SARS-CoV and MERS-CoV. What could be expected from the SARS-CoV-2?

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Abstract

Emerging viruses description have grown at an unprecedented rate since the beginning of the 21st century. The emergence of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and its related illness, Coronavirus Disease 2019 (COVID-19) has been reported as the third highly pathogenic coronavirus introducing itself into human population in the current era after the SARS-CoV and Middle East Respiratory Syndrome (MERS-CoV). Molecular and cellular studies considering the pathogenesis of this novel coronavirus are still in the early stages of research, however, regarding the similarity of SARS-CoV-2 and other coronaviruses, it could be hypothesized that the NF-κB, Cytokine regulation, ERK, and TNF-α signaling pathways are the more likely causes of inflammation upon onset of COVID-19. There are several drugs prescribed and used to alleviate the activity of these inflammatory cellular signaling pathways which might be beneficial for developing novel therapeutic modalities against COVID-19. In this review, we briefly summarized the alteration of cellular signaling pathways affected by coronavirus infection, particularly SARS-CoV and MERS-CoV and tabulated the current therapeutic agents approved for previous human diseases.

Keywords: SARS-CoV-2; COVID-19; coronavirus; signaling pathway; molecular alteration

Introduction

Emerging viruses description have grown at an unprecedented rate since the beginning of the 21st century [1]. More than 100 years after the start of the 1918 influenza pandemic, we now experience another pandemic. The emergence of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has been reported as the third highly pathogenic coronavirus introducing itself into human population in the current era after the SARS-CoV and Middle East Respiratory Syndrome (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 for their possible threat to the global health security. SARS-CoV has spread to several countries and led to more than 8000 cases and more than 750 deaths [5,6]. Also, MERS-CoV has resulted in more than 600 deaths caused by 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 for its benefit [10]. Interfering with signaling pathways which regulate processes such as DNA repair and replication, immune response, transcription, metabolism, cell cycle and survival; is one of the ways 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 the current research reports, PI3K/AKT, interferon, p38 MAPK, EGFR and NF-κB signaling pathways are altered following virus infection. The aforementioned pathways are involved in antagonizing the host antiviral response and vital for viral replication, entry, propagation, and apoptosis. Coronaviruses manipulate the molecular function of signaling pathways and this kind of interaction between host cell and virus might be responsible for an effective viral pathogenesis [13,14].

Rapid intervention in the usual public health behaviors, and the development of anti-viral compounds, antibodies, or vaccines are the keys for controlling the spread of a new virus and associated disease. MERS-CoV, SARS-CoV and SARS-CoV-2 are betacoronaviruses and therefore, share similar characteristics, but exhibit significant differences in their epidemiology, pathology, genetic, and protein composition. SARS-CoV-2 has around 79% genomic identity with SARS-CoV and nearly 50% with MERS-CoV [15,16]. According to these similarities, prior information in controlling SARS-CoV and MERS-CoV can guide and enhance our grasp of the pathogenesis and epidemiology of SARS-CoV-2 and the improvement of therapeutic approaches to control viral infection.

This review proposes a comparative outlook among MERS-CoV, SARS-CoV, and the recently epidemic SARS-CoV-2, in the interest of increasing the understanding of the interaction of host-pathogen, signaling pathways of the host, and immune evasion mechanisms of the pathogen. This analytical outlook may support in planning new treatments for COVID-19 soon.

Coronavirus structure and life cycle

Tyrrell and Bynoe reported the isolation of a virus from the respiratory tracts of adults with symptoms of common cold. This virus was shown to have an ability to grow in human embryonic tracheal tissue culture and to induce cold when inoculated in healthy volunteers [17]. During the same period, Hamre and Procknown showed that an unknown virus obtained from samples taken from medical students complaining from cold could persist and infect tissue culture. This virus was further called 229E [18]. These two novel respiratory viruses had not well-studied properties of orthomyxoviruses or paramyxoviruses. They shared similar and remarkable crown-like extra-membrane projections revealed by electron microscopy, according to Almeida and Tyrrell [19]. Subsequent consideration of these viruses with other contemporaneously discovered viruses including infectious bronchitis virus , transmissible gastroenteritis virus of swine, and mouse hepatitis virus (MHV) introduced a new viral group named coronavirus, in reference to their crown-like surface projections [20]. So far, numerous coronaviruses have been identified and among them, seven contribute to human diseases with clinical expression ranging from asymptomatic or mild to lethal infections. Taxonomically, the *Nidovirales* order contains a family called *Coronaviridae* and in turn, this family includes the *Coronavirinae* subfamily, which comprises the *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus* genera. Among these genera, there are several viruses with the ability to infect human cells and especially epithelial cells (ICTV or International Committee on Taxonomy of Viruses). Human coronaviruses (HCoV) belong to *Alpha*- and *Betacoronavirus* and encompass 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 new member of the *Coronaviridae* family, the new pandemic Coronavirus Disease 2019 (COVID-19) relevant agent, SARS-CoV-2 [23], which may induce severe syndromes. SARS-CoV2 and SARS-CoV both belong to the *Sarbecovirus* sub-genus within *Betacoronavirus* which also contains four others sub-genera : *Merbecovirus* (MERS-CoV), *Nobecovirus*, *Embecovirus* (HCoV HKU1, MHV, HCoV OC43, BCoV) 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 (Figure 1). In comparison with the other RNA viruses, this virus is a large (approximately 120 nm) one encompassing a single-stranded helical RNA, positive-sense combined with the Nucleocapsid (N) proteins [24]. Besides its viral assembly roles, N protein can adjust the coronavirus replication and the infected-cell response [25]. The next layer of coronavirus particle contains the major structural proteins or so-called Membrane (M) proteins functions to stabilize and maintain the viral envelope. The last structural protein, Envelop (E) protein, is the smallest one and plentifully expressed in the coronavirus-infected cell in contrast with its low participation in the virion [26]. The coronavirus RNA with a size ranging from 26.4 to 31.7 Kb contains genes coding for structural and non-structural proteins. The genome is organized as following : 5'-leader-UTR-replicase/transcriptase-S-E-M-N-UTR-3'-poly (A) tail; the replicase gene encodes the non-structural proteins proceeding the viral replication and facilitating its life cycle [27].

The coronaviruses replication is started following the S protein binding to its receptor on the host cell via the receptor-binding domain (RBD). The interaction of S and receptor determines not only which species could be infected but also which tissue could be involved in this infection [28]. The most abundant receptors used by coronaviruses are peptidases and it is shown that this binding is independent of the enzymatic domains of these peptidases. The receptors utilized by alphacoronaviruses such as HCoV-229E is usually the aminopeptidase N (APN) [29], while ACE2 (angiotensin-converting enzyme 2) is mostly used by HCoV-NL63 [30], SARS-CoV [31], and the newly discovered coronavirus, SARS-CoV-2 [32]. CEACAM1 (Carcinoembryonic antigen-related cell adhesion molecule 1) is employed during the entry stage of MHV [33], and MERS-CoV attaches to its host cell via binding to dipeptidyl-peptidase 4 (DPP4) [34]. The next step in a coronavirus infection is the entry of the virus within the host cell, mediated by S protein cleavage via the activation of cathepsin, Transmembrane Serine Protease 2 (TMPRSS2), or by other proteases in an acid-dependent manner resulting in the virus fusion into host cell membrane and injection of viral RNA into the cytosol (Figure 2) [35]. The viral genomic RNA recruits the protein production machinery of the host cell translating its replicase gene which has two open reading frames (ORFs), rep1a, and rep1b, into two general polyproteins called pp1a and pp1ab. All the non-structural proteins (nsps) are originated from such polyproteins as follows, pp1a and pp1ab cleavage results in the production of nsp 1-11 and nsp 1-16 respectively [36]. The cleavage of such polyproteins is mainly performed by viral proteases encoded in coronavirus RNA, such as the papain-like protease (PLpro) produced from nsp3 or Mpro produced by nsp5. Surprisingly, MERS-CoV, SARS-CoV, and also

SARS-CoV-2 only express one type of PLpro, however the other express two types [37,38]. Beside the direct translation of replicase gene and production of nsps to initiate replication and transcription of structural protein, the viral RNA is molded to synthesize genomic RNA and sub-genomic RNA for the forming of a complete virion. Such sub-genomic RNA are translated into the coronavirus structural proteins E, S, and M which are transmitted to ER (endoplasmic reticulum) and then extracted from the ER system as the ER-Golgi intermediate compartment (ERGIC) [39]. This kind of endosome is now ready for the incorporation with the encapsidated viral genomic RNA producing and releasing a mature virion from the infected-cell. For this purpose, the N protein is translated from sub-genomic RNA joining with new synthesized viral genomic RNA and budding within the ERGIC [24]. Eventually, the mature virion is transported on the cell surface and release via exocytosis.

Coronavirus and host molecular modifications

NF-κB

NF-κB (Nuclear factor-kappa B) is one of the important family of transcription factors that can enhance the transcription of stress-response proteins and pro-inflammatory cytokines and chemokines. In the cytoplasm, an inhibitor of κB (IκB) binds to NF-kB and causes inactivation of NF-kB [40]. Cellular stimuli trigger the degradation, ubiquitination, and phosphorylation of IκB through the proteasome and arouse NF-κB translocation. In fact, NF-κB activation has a crucial role in the inflammatory response against respiratory viruses such as human coronaviruses [41]. It has been reported that several structural and non-structural proteins of SARS-CoV including N protein, S protein, nsp1, nsp3a, and nsp7a can stimulate the NF-kB activation [42]. As a response to the SARS-CoV infection, as a stress-inducing condition, enhanced secretion of IL-1β are 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 inflammasome [43].

Regarding the ability of NLRP3 (NLR Family Pyrin Domain Containing 3) to facilitate the oligomerization of ASC (apoptosis-associated speck-like protein containing CARD) and to activate inflammasome, SARS-CoV E protein, ORF3a and ORF8b were proved to be the activators of NLRP3 inflammasome. ORF3a and E protein can inspire the NF-κB activation required for pro–IL-1β gene transcription. Besides, E protein through Ca^{2+} transport caused activation of NLRP3 inflammasome [44]. SARS-CoV ORF3a accomplishes these phenomena through the TRAF3 (TNF receptor-associated factor 3)-dependent ubiquitination of p105. Moreover, different mechanisms advocate that SARS-CoV ORF3a promotes assembly of NLRP3 inflammasome via TRAF3-dependent ku3 ubiquitination of ASC [45]. 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 required to prove this [45].

During the MERS-CoV infection, o4b protein binds to the karyopherin-α4 (importin-α3) resulting in the inhibition of its interaction with NF-κB-p65 and gives rise to hindrance of the nuclear translocation of NF-κB. Accordingly, the expression of pro-inflammatory cytokines as well as NF-κB-dependent cytokines increases as a result of latter event (Figure 3) [41].

Lately, it has been indicated that SARS-CoV-2 nsp13 could interact with several transducin-like enhancer (TLE) family proteins regulating the inflammatory response of NF-kB. Also, ORF9c can moderate IκB kinase activity and NF-κB signaling pathway via the interaction with NDFIP2, NLRX1, F2RL1 [46].

TGF-β

TGF- β (Transforming growth factor- β) 1 is a kind of cytokine binding to the TGFbRI and TGFbRII serine-threonine kinase receptors through the TGF-β signaling pathway and results in the activation of SMAD-dependent and SMAD-independent paths [47]. TGF-β1 is a moderator 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 could target TGF-β signaling in several types of cells [48].

During the SARS-CoV infection, through the ROS / p38 MAPK / STAT3 axis correlating with the elevated pro-fibrotic responses, the PLpro induces Egr-1 dependent TGF-β1 promoter activation [49]. Also, another study has indicated that SARS-CoV PLpro upregulates the expression of type I collagen via SMAD-independent TGF-β1

signaling leading to the pro-fibrotic responses in the lung [50]. SARS-CoV N protein promotes the complex construction of the SMAD3-p300 complex, however, it could inhibit the activation of SMAD3 and SMAD4-mediated apoptosis in the infected cells. These results reveal an interesting effect of the N protein of SARS-CoV hampering the incidence of apoptosis in the host cells and promoting tissue fibrosis and also propose the novel strategies for the treatment of SARS by targeting the TGF-signaling compartments [51]. The MERS-CoV, as another human lethal coronavirus, could prompt the apoptosis of kidney and lung cells through the upregulating of SMAD7, an important protein in the TGF-β signaling pathway (Figure 3) [52]. Given the likely resemblance of SARS-CoV-2 and SARS-CoV, it could be predicted that the COVID-19 causative agent can also affect the TGF-β signaling pathway during its infection in humans.

Cytokine regulation

Macrophages play critical roles in the immune system through cytokine regulation pathway and phagocytosis in response to coronaviruses infection. Actually, these innate immune cells are the main sources of cytokines within the patient's body [53]. An immunological and serological study done on the SARS patients had indicated the low level of antiviral cytokines (IL-12p40 and IFN-α/β/ γ) and upregulated pro-inflammatory cytokines (IL-6 and TNF-α) as well as the increased level of inflammatory chemokines such as macrophage inflammatory protein 1 α (MIP-1α). The insufficiency of antiviral cytokines in addition to the extreme upregulation of inflammatory chemokine could show a mechanism for escaping of SARS-CoV from the immune responses [54]. It has been 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 the cells which are SARS-CoV-infected ACE2+ [48].

Additionally, SARS-CoV PLpro is able to inhibit the production of type I interferons and pro-inflammatory cytokines through the activity of Toll-like receptor (TLR) and retinoic-acid inducible gene I (RIG-I) paths. This viral protein remarkably impeded the manufacture of imiquimod-induced cytokine utilizing the suppression of NF-κB, activator protein 1 (AP-1), and interferon regulatory factor 3 (IRF-3) expression [55]. As mentioned before, NF-κB can be translocated to the nucleus leading to higher pro-inflammatory cytokine expression [41]. It has been reported that, SARS-CoV ORF8b might also has a critical role in the inflammasome activation and cytokine storm and triggers NLRP3 activation as well as releasing of the IL-1β [56].

Higher inflammatory cytokine/chemokines expression such as the elevated level of CXCR3, IL-8 (CXCL8), SOCS5, IL-1β, CCR2, and IL-1α confirmed the lung immunopathology in the lower respiratory tracts of the patients who are MERS-CoV-infected that along with the decreased Th1 and Th2 probably results in a severe infection, increased case death, immunopathology and lung inflammation (Figure 3) [57].

The modification of cytokine regulation pathways' upstream might be a successful strategy for COVID-19 treatment. It is suggested that more attention must be paid to the dysregulated production of IFN-I in COVID-19 patients as well as to thoughtful ALK, cGAS, and STING as the targets for the treatment against cytokine storm which occurs in acute cases of SARS-CoV-2 and SARS-CoV [58].

p53

One of the key regulators of the cell cycle activated in response to different types of stress through phosphorylation changes and other post-translational modifications such as acetylation is transcription factor p53 [59,60]. The upregulation of p53 increases expression of genes involved in DNA repair (Gadd45α, P53r2, Ddb2, Mgmt), apoptosis (Bax, Noxa, Puma, Pig3) or cell-cycle arrest (14-3-3σ, p21, Btg2, Reprimo), when the damage is irreversible [60,61]. Also, the level of p53 protein in the cell is controlled by MDM2 and MDMX factors. These two factors together reduce intracellular p53 by activating the E3 ubiquitin ligase and ultimately leading p53 to degradation by the proteasome [62,63]. The p53 acts as a tumor suppressor in cancer cells. Besides, recent reports suggest that p53 can act as an antivirus and assists cellular immune responses to eradicate pathogens like viruses [64]. Therefore, as a type of cellular stress, viral infections stimulate the host cell-activating p53 in virus-infected cells that eventually can induce apoptosis and suppress viral replication [65-67]. Extensive studies show that p53 is expressed as a response to viral infections enhances the expression of genes; interferon-stimulated genes (ISG15), interferon regulatory factors (IRF9/5/7) and toll-like receptor (TLR3) which are involved in typ1 IFN-dependent antiviral response [64,66,68]. Several studies have revealed that p53 could have both positive and negative impacts on various viral infections. Thus, recent observations indicated that p53-dependent apoptosis is detrimental in the early stages of replication for some viruses, but in late stages of replication, some viruses use apoptosis to transmit formed viral particles to other healthy cells [69]. Previous studies have observed that Fusion (F) protein of the RSV induces p53-dependent apoptosis. Besides, RSV-M protein stimulates an arrest during the cell cycle of lung epithelial cell by activating p53 pathway

[70,71]. Recent research has reported that p53 is involved in the induction of apoptosis and IFN production of during influenza virus infection and prevents virus replication [72]. Moreover, p53 induces IFN signaling and reduces Transmissible gastroenteritis virus (TGEV) replication during viral infection [73]. On the other hand, PEDV (porcine epidemic diarrhea virus) infection and MHV (murine coronavirus mouse hepatitis virus) induces cell cycle arrest by activating the transcription factor p53 that beneficially contributes to viral infection [74,75]. Previous studies have also illustrated that SARS-CoV 3a protein leads to the cell cycle arrest via increasing phosphorylation of p53 [76].

Lin Yuan *et al.* demonstrated that PLpro of the HCoV-NL63 inhibits p53-dependent antiviral response by reducing the stability of the p53 transcription factor via increasing the MDM2-mediated ubiquitination which ultimately leads to enhanced virus replication [77]. Furthermore, Yue Ma-Lauer *et al.* revealed that in the family members of coronavirus such as MERS-CoV and SARS-CoV , p53 acts as a negative regulator and reduces virus replication. The research proposes that the nsp3 has the protective domains of the SARS-unique domain (SUD) and PLpro that act to counteract the antiviral effect of p53. To this end, SUD and PLpro together destroy p53 and inhibit the host cell's defense response by stabilizing E3 ubiquitin ligase RCHY1 [78]. 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 [79]. Recent clinical studies report that SARS-CoV2 infection may cause apoptosis of lymphocytes. Interestingly, in patients with lymphopenia, p53 (an important factor associated with apoptosis), is significantly increased [80]. Compared to other coronaviruses such as MERS-CoV and SARS-CoV, it has been shown that SARS-CoV-2 is more sensitive to type 1 IFN-dependent antiviral response in the early stages of infection [81]. Since p53 plays a critical role in inducing type 1 IFN-dependent antiviral response, it is destroyed by MERS-CoV and SARS-CoV. The SARS-CoV-2 may also inhibit antiviral responses by destroying p53. Moreover, MERS-CoV and SARS-CoV use p53 signaling to induce apoptosis and cell cycle arrest, maybe SARS-CoV2 uses the p53 pathway to induce cell cycle arrest and apoptosis (Figure 3).

EGFR

EGFR (Epidermal growth factor receptor) belongs to the family of receptor tyrosine kinases (RTKs) in transmembrane, which has an extracellular domain for ligand binding and an intracellular domain. They regulate many

cellular processes by activating downstream signaling pathways such as PI3K/Akt, Ras/Raf/MAPK, STAT, and Src Kinase pathway via phosphorylation [82]. The up-regulation of this pathway has been seen in many cancers that increase cell migration and proliferation. The over-activation of EGFR upon a viral infections has a major role in the entry of the virus into the host cell producing more mucus and activating the inflammatory response [83,84]. Recent reports suggest that EGFR and PI3K/Akt downstream signaling stimulate uptake of Influenza A virus (IAV) into the host cell [85]. In contrast, inhibition of EGFR and viral neuraminidase (NA) protein alone or in combination with other drugs reduces the invasion and the release process of IAV [86]. In addition, another research reported that in the early stages of viral infection, EGFR acts as a co-factor for the entry of the Transmissible gastroenteritis virus (TGEV) and has a synergistic role with the Aminopeptidase N (APN) receptor in the cell membrane [87]. PEVD infection activates EGFR and the STAT downstream signaling pathway that leads to inhibition of type I interferon antiviral response [88]. Furthermore, Iris F. Ueki *et al*. observed that respiratory viral infections suppressed epithelial antiviral responses IRF1-dependent interferon-λ by increasing the activity of the EGFR signaling pathway. In contrast, inhibition of the EGFR signaling pathway reduces viral infection by increasing the activity of the host cell antiviral responses [89,90]. 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 stimulate macropinocytosis, which occurs late during infection [91]. Extensive studies have reported that the EGFR signaling pathway acts critically in the progression of lung fibrosis [92]. One of the main causes of pulmonary fibrosis is acute infection caused by respiratory viruses such as SARS-CoV. 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 infections have a high risk of developing pulmonary fibrosis. EGFR signaling is an important regulator of the SARS-CoV-induced lung damage. Hence, researchers suggest that the up-regulation of the EGFR pathway after SARS-CoV infection increases fibrosis [93]. Activation of EGFR regulates downstream signaling pathways such as Akt, PI3K and ERK which are involved in inducing 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 excessive fibrotic response to SARS-CoV (Figure 3) [93,94]. SARS-CoV-2, as other emerging respiratory viruses, may induce pulmonary fibrosis in survivors of SARS-CoV-2 infection by activating the EGFR pathway. SARS-CoV2 leads to pulmonary injury and EGFR might facilitate its entry to the host cell and causes inflammatory responses. Therefore, understanding how EGFR functions after a viral infection may lead to new treatments in the future.

JNK

C-Jun NH2-terminal kinases (JNK1/JNK2) signaling is a mitogen-activated protein kinase (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 activator protein-1 (AP-1) transcription factor is [95,96]. Research shows that JNKs are important kinase proteins that are activated in innate immune responses to viral infection and stimulate the activity of several significant cytokines, such as Interleukin (IL-2, IL-4) and Interferon-gamma (IFNγ) [97]. Influenza A virus (IAV) infection activates the AP-1 transcription factor by activating the JNK signaling pathway during the early life cycle, which appears to be related to the innate immune response to infection [98]. Besides, recent reports indicate that Respiratory syncytial virus (RSV) infection increases IL-33 levels in lung macrophages through MAPK and JNK1/2 signaling pathways [99]. Also, recent reports suggest that the Respiratory virus (RSV) infection may induce severe pneumonia by activating the JNK/AP-1 signaling pathway [100]. Furthermore, the coronavirus infectious bronchitis virus (IBV) stimulates the activity of the JNK signaling pathway by activating MKK7, which ultimately increases virus-induced apoptosis. Paradoxically, inhibition of the JNK signaling pathway by SP600125 eliminates the inhibitory effect of JNK on the Bcl2 anti-apoptotic protein, which ultimately reduces apoptosis during IBV infection [101]. Up-regulated Bcl-2 or other anti-apoptotic proteins protect cells against coronavirus-induced apoptosis such as severe acute respiratory syndrome (SARS-CoV) [102,103]. Another study found that the JNK signaling pathway is activated during HCoV-229E infection and plays an anti-apoptotic role through modulation of Bcl2 family proteins. Activation of JNK also regulates innate immunity by inducing interferon β (IFNβ) and interleukin-8 (IL8) [104]. Moreover, JNK signaling pathway plays an crucial role in SARS-CoV infection. Hence, the phosphorylation of JNK and its upstream pathways have been seen 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 [105,106]. Moreover, the N protein of SARS-CoV is involved in the apoptosis induction through the JNK activation and p38 MAPK signaling pathways in the absence of growth factors [107]. Also, Zhongde Ye *et al.* observed that the encoded protein

by open reading frame (ORF6) of the SARS-CoV genome induces apoptosis by Caspase-3-mediated endoplasmic reticulum (ER) stress and JNK-dependent signaling pathways [108]. Up-regulation of SARS 3a and 7a protein has also been demonstrated to induce JNK activation [109]. Furthermore, SARS-CoV 3b protein stimulates the expression of the AP-1 transcription factor by activating JNK and ERK signaling pathways. Activated AP-1 by 3b protein stimulates the pro-inflammatory cytokines that are involved in cytokine storm production during pathogenicity of SARS-CoV (Figure 3) [110]. According to the mentioned findings in SARS-COV, JNK and its upstream signaling pathways, such as MKK4 and MKK7 could have a major part in SARS-CoV2-induced apoptosis. SARS-CoV2 like SARS-CoV may produce pro-inflammatory cytokines through AP-1 activation in response to the infection.

p38 Mitogen-activated protein kinases (MAPK)

The p38 MAPK family comprises four groups of 38 kDa protein (p38) [111]. It is activated by phosphorylation on Thr180-Gly-Tyr182, called activation loop, when exposed to a virus infection, growth factors, environmental stresses such as viral infections, and inflammatory cytokines [111,112]. The p38 MAPK signaling pathway has various kinds of roles depending on the type of stimulation and also the type of tissue exposed to such stimulation. Hence, p38 MAPK signaling increases cell death and survival [113,114]. Its key role has been observed in many viral infections which cause respiratory symptoms: in HCoV-229E the activation of p38 MAPK is needed to induce CPE (cytopathic effect) and viral replication [115]. Mouse hepatitis virus (MHV, also known as murine coronavirus) for duplication needs p38 MAPK activation and its activation leads to the eIF4E phosphorylation to translate host cell's proteins, such as IL6 to synthesize virus-specific protein [116]. Influenza A Virus (H5N1) highly activates p38 MAPK to induce cytokines [117]. Influenza virus (IV) infection stimulates apoptosis and cytokines production. P38 MAPK is activated in the result of IV infection in human bronchial epithelial cells (BEC) [118]. Moreover, the H1N1 influenza virus, another type of Influenza A, ligation to Toll-like receptor 4 (TLR4) triggers p38 MAPK activation through the expression of MyD88 and it is necessary for virus entry in 1HAEo-, human airway epithelial cell lines [119]. Avian Infectious Bronchitis Virus (IBV) by p38 MAPK phosphorylation causes IL6 and IL-8 production, on the other hand, Dual-specificity phosphatase 1 (DUSP1), as a protein phosphatase, in the cells infected with IBV is upregulated to dephosphorylate p38 MAPK in order to regulate pro-inflammatory cytokine [120].

In SARS-CoV infected cells the p38 MAPK is phosphorylated through downstream effectors such as STAT3 (signal transducer and activator of transcription 3), MAPK activates protein kinase 2 (MAPKAPK2), eIF4E (eukaryotic Translation Initiation Factor 4E) and activating transcription factor 1 (ATF-1) [121-123]. SARS-CoV-infected Vero E6 cells manifest an enhanced level of phosphorylated p38 MAPK [123]. Moreover, 3a protein of SARS-CoV increases p53 level leading to the p38 MAPK activation and the upregulation of *Bax* expression which consequently triggers the intrinsic apoptosis pathway [79]. The SARS-CoV induces apoptosis to cause intense damage in the lung tissue which is one of the prominent symptoms of this disease [124]. Besides 3a protein, 7a protein not only activates apoptosis through activating p38 MAPK but also inhibits translation [125]. Moreover, the N protein of SARS-CoV in COS-1 monkey kidney cells stimulates apoptosis via p38 MAPK upregulation [107]. In SARS-CoV, TGF-β1 is upregulated through the Egr-1-mediated pathway which is induced by papain-like protease (PLpro). The TGF-β1 prompts lung fibrosis both in mouse and human lung tissues through ROS/p38 MAPK/STAT3 pathway triggered by SARS-CoV PLpro [49]. During SARS-CoV infection, syntenin activates p38 MAPK to increase inflammatory cytokines [126]. Recombinant SARS-CoV lacking envelope protein (E) PDZ-binding motif (PBM, a domain connected with protein-protein interactions) has a lower amount of p38 MAPK, suggesting that E protein is involved in the severity of the infection [126]. Increased level of phosphorylated p38 MAPK in SARS patients provides high levels of IL-8 and aberrant cytokines [127]. Moreover, an *in vitro* experiment showed that the p38 MAPK inhibitor had an antiviral outcome against MERS-CoV (Figure 3) [128].

As mentioned, SARS-CoV proteins such as 3a, 7a, N, and E are involved in activating p38 MAPK, suggesting that SARS-CoV2 proteins may also be involved in triggering p38 MAPK signaling pathway. One of the well-known symptoms of coronavirus 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-CoV2 likely uses p38 MAPK signaling to lead to apoptosis and lung damage.

ERK

ERK (The extracellular signal-regulated kinase) is one of the main members of the MAPK (mitogen-activated protein kinase) signaling pathways [129]. ERK1, ERK2 also referred to the p44/42 MAPK that are involved in cell proliferation, survival, motility, and differentiation when exposed to mitogens and extracellular stimulant [130,131].

The ERK pathway activation depends on the Ras binding to the cell membrane to initiate the cascade and ERK phosphorylated on Thr183-Glu-Tyr185 then it is translocated to the nucleus [132-134].

An earlier study shows that ERK1/2 and MEK1/2 knockdown prevents the replication of the murine coronavirus genome but don't affect protein translation and the virus entry [135]. Human respiratory syncytial virus (RSV) through Raf/MEK/ERK-dependent signaling infects the host cell. ERK is activated in two-phase: the early activation in RSV-infected cell is related to virion binding [136] and the late activation is essential for protein F secretion that is required for RSV replication [137]. Endothelin-1 (ET-1) is up-regulated in pulmonary fibrosis, induces the MEK/ERK MAP kinase pathway and increases CCN2 mRNA and protein level [138]. In Idiopathic pulmonary fibrosis (IPF), TGFβ-1, through the ERK1/2 pathway, stimulates human lung fibroblasts transformation into myofibroblasts [139,140]. It also increases α-SMA and collagen expression in the lung via activating ERK1/2, inhibiting GSK-3, and β-catenin translocation to the nucleus [141]. In the swine influenza virus (SIV, H1N1pdm) as an acute respiratory disease that infects pigs, ERK1/2, JNK1/2, and p38 MAPK is phosphorylated and activated. ERK1/2 activation is necessary for cellular responses because of the infection and TNF-α, IFN-β, IL-6, IL-8, and IL-10 production in swine macrophages [142]. Moreover, ERK induces NFκB activation in SIV-infected cells [142]. ERK in H9N2 avian influenza virus inhibits FasL and TNF-α to suppress extrinsic apoptosis [143].

Not only p38 MAPK but also ERK1/2 are phosphorylated and activated in Vero E6 cells infected with SARS-CoV [123]. P90RSK, as a downstream element of ERK, phosphorylated in Ser380 via p38 MAPK, plays a major role in SARS-CoV-infected cells; in the case that its Thr573 phosphorylation is decreased [144]. The p90RSK controls apoptosis and is resulted from the treatment of SARS-CoV infected Vero E6 cells with PD98059 (ERK inhibitor) and SB203580 (p38 inhibitor) showing that p38 inhibitor reduced p90RSK phosphorylation. However, ERK inhibitor could not cause any remarkable change to rescue the infected cell from horrible injury [144]. Thus, ERK phosphorylation is not adequate to obstruct apoptosis with the infection induced by SARS-CoV, due to Akt slight activation in the cells that are virus-infected [145].

Moreover, Surjit *et al*. demonstrated that in COS-1 cells SARS-CoV N protein induces apoptosis via ERK down-regulation in the cells free from growth factors [107]. AP-1 controls cytokine transcription due to the SARS-CoV infection and ERK activation upregulates AP-1 activity via c-Fos [110]. Besides, 3b, as one of the accessory proteins of SARS-CoV [146] stimulates AP-1-related genes [110]. ORF3b by activating ERK pathways prompts AP-1

transcriptional activity [110]. SARS-CoV with S, PLpro, 3b proteins, and MERS-CoV via Raf/MEKK2,3/Mos and then MKK1,2,5 induce ERK signaling pathway [104]. Furthermore, ERK/MAPK pathway along with PI3K/AKT/mTOR pathway plays a crucial role in the pathogenesis of MERS-CoV and its inhibitors prevent MERS-CoV proliferation *in vitro* [147]. Taken together, the ERK signaling pathway is essential for pathogenicity, avoiding host cell apoptosis, and causing lung injury and viral spread. COVI-19 leads to the releasing of pro-inflammatory cytokines, such as interleukin (IL)-1β and IL-6 to provoke lung inflammation, fever, and fibrosis [148]. As it is mentioned above, the ERK stimulates AP-1 activation through 3b and ORF3b viral proteins to increase cytokines expression and via N protein increases survival in the host cell infected with in SARS-CoV (Figure 3). Moreover, it is almost predictable that ERK could activate AP-1 and cytokine expression in SARS-CoV-2.

TNF-α

TNF-α (tumor necrosis factor α) belongs to the TNF superfamily of transmembrane proteins which is a proinflammatory cytokine and mainly secreted from macrophages [149]. Its essential roles in facing pathogens are immune-regulation, inhibition of infection factors, and tumors [150,151]. *TNF-α* is associated with many diseases due to its specific locus location [152]. This cytokine mediates the inflammatory response and is important for the host cell defense against pathogens and its excessive expression can exacerbate the disease [152]. Each person has a different ability to produce cytokines that are related to their genetic background [153]. TNF-α correlates with autoimmune diseases, such as rheumatoid arthritis, inflammatory bowel disease, psoriasis, and refractory asthma [154]. It has various effects, for instance, it increases pro-inflammatory release, enhances adhesion molecules, and increases eosinophils and neutrophils' migration. Moreover, its elevation has been observed in the mice infected with B1 human adenovirus [155] and in the humans infected with influenza H1N1 [156]. The capsid of Hepatitis B virus highly induced TNF-α in THP-1 macrophages of human [157]. TLR2 (Toll-like receptor 2) activation by binding to viruses, such as HCV [158], measles virus [159], and various herpesviruses like herpes simplex virus (HSV) [160] and cytomegalovirus [161] is followed by TNF-α production. TNF-α is associated with lung fibrosis [162] and pulmonary fibrosis [163] which together with IL-1 is overexpressed in regenerating Type 2 pneumocytes in the lung [162]. In IPF progression, epithelial cells release cytokines, such as TNF-α that develop the fibroblasts transformation into myofibroblasts and induce extracellular matrix molecules production leading into respiratory inadequacy [164].

In SARS patients, a high amount of TNF-α has been detected which suggests TNF-α is involved in SARS pathogenesis [165] through extreme inflammation [166]. The TNF-α level is significantly increased in the acute stage and reduced in the convalescent stage of illness in SARS patients [167] which suggests that TNF-α plays a pivotal role in the pulmonary injury triggered by SARS coronavirus, and its inhibitors can be a potent factor in acute respiratory disease syndrome treatment initiated by coronavirus [168]. SARS-CoV S protein attaches to the host cell receptor to cause infection [31]. The S protein induces IL-6 and TNF-α production via NF-κB pathway activation in RAW264.7 cells, murine macrophages [169]. Moreover, p38 MAPK activation gives rise to TNF-α and IL-6 production [170,171]. It is thought that RAW264.7 incubation with S protein activates the p38 pathway thus enhances TNF-α and IL-6 level [169]. Additionally, SARS-CoV in dendritic cell (DC) and human macrophage (Mφ) induces TNF-α and IL-6 production [54,172]. Haga *et al.* demonstrated 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 to assist viral entry and tissue injury [173]. TACE continuously sheds ACE-2 in the epithelial of the human airway to release soluble ACE2 (sACE2) which is active [174]. There is no evidence that TNF-α obstruction is dangerous for COVID-19 patients [154]. The TNF-α has high levels in immune response cells, such as dendritic cells and macrophage in SARS-CoV-infected cells to prevent infection. In addition, TNF-α intensifies SARS-CoV infection symptoms like lung tissue injury and facilitates virus entry (Figure 3). It is reported that SARS-CoV-2 causes severe pulmonary damage which amplifies the theory that TNF-α worsens the symptoms of the SARS-CoV-2, promotes overproduction of cytokines by the S protein, and TACE may also be involved the entry of SARS-CoV-2.

Interferon signaling pathway

The immune system supports the body against infections and the innate immune response is the first step of protection against pathogens [175]. In viral infections, it stimulates the interferon (IFN) signaling pathway and ultimately the type I IFN (IFN-I) expression, which leads to an antiviral response in the cells [176]. IFN-Is bind to cell surface co-receptors and stimulate the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling network and upregulate several IFN-stimulated genes (ISGs). Numerous of the proteins encoded by these ISGs are responsible for antiviral functions [177]. However, viruses have developed various mechanisms to interfere with IFN expression and this appears to apply to coronaviruses (CoVs). In SARS-CoV, MERS-CoV, and other types of CoVs,

the response to viral infections through IFN-Is is hampered. These CoVs use different mechanisms to lessen the IFN-I generation. This suppression strategy is closely related to disease severity and mortality [178].

TGEV (Transmissible gastroenteritis virus) escapes the IFN-I response through IRE1α-based manipulation of the miR-30a-5p/SOCS1/3 Axis as a member of the alphacoronavirus family. TGEV prevents host miR-30a-5p through the ER stress sensor Inositol-requiring transmembrane kinase/endoribonuclease 1α (IRE1α), resulting in the augmented expression of negative regulators of JAK-STAT signaling pathway including Suppressor of cytokine signaling 1 (SOCS1) and SOCS3. Augmented SOCS1 or SOCS3 expression weakened the IFN-I antiviral reaction, supporting TGEV replication [179]. Recent researches 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) stopped TRIM25- mediated RIG-I ubiquitination, which led to the suppression of IFN generation [180,181]. Also, Lui *et al.* propose 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 [182]. A recent study reveals SARS-CoV proteins 8ab and 8b as new IFN antagonists. This study demonstrated the direct association of these two proteins with IRF3. It was also found that these two proteins moderately inhibit IFN stimulation by restricting IRF3 activation and by increasing the proteasome-dependent destruction of IRF3 [183]. Also, Lee *et al.* state 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 [184].

Moreover, the expression of the membrane-anchored PLpro domain (PLpro-TM) from SARS-CoV prevents STING/TBK1/IKKε-based stimulation of IFN-Is 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 TNF receptor-associated factor 3 (TRAF3), TBK1, IκB kinase ε (IKKε), STING, and IRF3, the significant factors that construct the STING-TRAF3-TBK1 complex for stimulation of IFN expression [185]. Yang and colleagues reported the recognition of the IFN antagonism strategy of MERS-CoV ORF4b. They presented 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 (Figure 3) [186].

The rapid appearance of SARS-CoV-2 has increased the investigation of innate immune responses to CoVs. Recent research reveals that SARS-CoV-2 stimulates insignificant expression of IFNs (type I, II, or III) in infected cells, even amongst coronaviruses. This lack of IFN generation probably impedes the primary innate immune response to SARS-CoV-2 infection and proposes that exogenous IFN treatment can be successful against SARS-CoV-2 [187]. Moreover, Lokugamage *et al.* indicate that SARS-CoV-2 has a great sensitivity to IFN-I compared to SARS-CoV. This augmented sensitivity to IFN-I is probably because of variations in viral proteins between the two CoV strains [188]. Finally, we predict that the IFN antagonisms of SARS-CoV-2 and their capacity to stop 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 other CoVs, which should be confirmed through future studies on SARS-CoV-2.

PI3K/AKT

The phosphatidyl-inositol-3 kinases (PI3K)/AKT pathway controls different cellular processes, such as antiviral immunity ,cell proliferation, protein translation, RNA processing, apoptosis, and autophagy [189]. In order to more successful replication, several host cellular signaling pathways were stimulated and exploited by virus infection. The PI3K/AKT pathway has newly fascinated significant attention because of its function in controlling virus replication. This pathways has been indicated to be essential not only for viral cell entry but also for following intracellular trafficking and viral replication for particular viruses [190]. Apoptosis signifies an operative antiviral mechanism for an infected organism, that is easy and most of the time 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 [191]. PI3K-Akt signaling is also related to an up-regulating interferon response and more PI3K/AKT activity can stop viral spread due to the initiation of cellular defenses [192]. Influenza virus stimulating this pathway controls an premature pace during viral entry, that decreases the IRF-3-based promoter function and weakens the dimerization of IRF-3 , therefore resulting in the host antiviral activity reduction [193]. Kindrachuk *et al.* revealed that in vitro MERS-CoV replication meaningfully stopped by a group of licensed kinase inhibitors targeting the PI3K/AKT/mTOR pathway. Thus, these data propose that PI3K/AKT/mTOR signaling has a central role in MERS-CoV infection and may indicate new drug targets for

treatment [147]. Also, it is found that PI3K/AKT signaling pathway is vital for starting insistant SARS-CoV infection in Vero E6 cells and no viable cells were detected after treatment with the PI3K/AKT inhibitor, LY294002 [194,106]. Moreover, Chan *et al*. found that M protein of SARS-CoV modulates the cellular AKT pro-survival pathway and mitochondrial cytochrome c secretion and stimulates apoptosis by means of it (Figure 3) [195].

According to the information obtained from previous COVs, we can predict that infection with SARS-COV2 stimulates PI3K/AKT signaling, also stopping P13K activation can lessen viral infection.

The likely dysregulated signaling pathways upon the infection of SARS-CoV-2

SARS-CoV-2 global crisis has reminded everyone that despite the public health concerns, viruses are genetically and functionally altered day by day to better infect different species, especially humans. Coronaviruses, on the one hand, functionally paralyze their host cells and, on the other hand, force them to produce their own essential proteins. In the meantime, many of the host cell's signaling pathways are undergoing several alterations, which could worsen the disease condition caused by these viruses. In the current review, we summarized information about several signaling pathways recruited by a coronavirus infection and illustrated the exact mechanisms during this event. Overall, the main purpose of a virus upon its entry into the host cell is to replicate its RNA/DNA, maintain or over-activate machinery of the protein production of the host cell, and evade from the immune responses by the host. Regarding the ability of coronavirus infections, particularly SARS-CoV-2, to induce inflammation and lung injury and also similarity of this novel virus with MERS-CoV and SARS-CoV to infect lung epithelial cells, it is expected that this emerging life-threatening coronavirus involves the same cellular signaling pathways as MERS-CoV and SARS-CoV. As a therapeutic approach, utilizing of anti-inflammatory agents during COVID-19 to affect on the inflammatory signaling pathways might be beneficial to reduce the severity of disease (Table 1). The NF-κB, Cytokine regulation, ERK, and TNF-α signaling pathways were shown to be more likely causes of inflammation during MERS-CoV and SARS-CoV as well as the incidence of neutrophilia and basophilia in SARS-positive patients exacerbating the disease condition [196]. Besides, the inflammatory cytokines level augmentation in the serum sample of COVID-19 patients shed a light in the involvement of such signaling pathways during 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 initiate to infect its host cell. Also, the researchers of molecular medicine should consider the roles of most up/downregulated ingredients of cellular

signaling pathways during COVID-19 to identify and design more beneficial molecular drugs decreasing the fatality of this novel pandemic coronavirus.

Conflict of Interest

The authors declare that they have no conflict of interest.

Author contributions

All authors contributed to the study conception and design. Data collection and categorization were performed by Zahra Asadzadeh, Noora Karim Ahangar, Hajar Alemohammad, and Basira Najafzadeh. The designing of figures was done by Amir Baghbanzadeh, Afshin Derakhshani, and Souzan Najafi. The English editing also was performed by Dr. Hossein Bannazadeh Baghi and Darya Javad Rashid. The first draft of the manuscript was written by Nima Hemmat and all authors commented on previous versions of the manuscript. The corresponding authors of the manuscript are Dr. Meriadeg Ar Gouilh and Dr. Behzad Baradaran. All authors read and approved the final manuscript.

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

Drug	Target	Main use	Refs
Sorafenib	jnk	suppresses hepatitis B virus gene expression	[197]
Berberine	jnk	inhibits coxsackievirus replication	[198]
SP600125	jnk	inhibits human cytomegalovirus replication, Anti-cancer	[199,200]
AS601245	jnk	Anti-Inflammatory, Anti-cancer	[201]
Ginsenoside Rg1	jnk	suppresses liver necrosis and inflammatory responses	[202]
BI-78D3	jnk	Anti-cancer	[203]
BX-795	Jnk/p38	inhibits HSV-1 and HSV-2 replication	[204]
Gefitinib	EGFR	Suppresses Respiratory Viral infection	[205]
AG148	EGFR	Inhibits Cell Proliferation and Arrests Cell Cycle	[206]
Erlotinib	EGFR	inhibits HBV replication, Anti-cancer	[207,208]
Lapatinib	EGFR	Anti-cancer	[209]
Afatinib	EGFR	preventing an excessive fibrotic response in SARS-COV and other respiratory viral infections	[93]
Rociletinib (CO-1686)	EGFR	Anti-cancer	[210]

pifithrin-α	P53	A Chemical Inhibitor of p53 That Protects Mice from the Side Effects of Cancer Therapy	[211]
2-sulfonylpyrimidine (PK11007)	mutant p53	PK11007 is a potential new treatment for triple-negative breast cancer (TNBC)	[212]
ReACp53	mutant p53	induces mitochondrial cell death and reduces DNA synthesis	[213]
SB 239063	P38 MAPK	lung fibrosis	[214]
SB202190	P38 MAPK	Renal fibrosis	[215]
SB203580	P38 MAPK	Hypothalamus Inflammation	[216]
BIRB796	P38 MAPK	Cervical Cancer	[217]
SB 239063 and SKF 86002	P38 MAPK	septic lung injury	[218]
FR180204	ERK	Cancer treatment	[219]
ERK5-IN-1	ERK	regulates MDR potential	[220]
etanercept, infliximab, adalimumab, certolizumab and golimumab	TNF-α	autoimmune diseases treatment such as, rheumatoid arthritis, Crohn's disease and psoriasis	[221]
celastrol	TNF-α	Represses infilimation and propagation in RAW264.7 cells	[222]
Triptolide	TNF-α	In differentiation of Osteoblast	[223]

Bithionol, Bortezomib, Cantharidin, Chromomycin A3, Daunorubicinum, Digitoxin, Ectinascidin 743, Emetine Inactive, Fluorosalan, Manidipine ,hydrochloride, Narasin, Lestaurtinib, Ouabain, Sorafenib tosylate, Sunitinib malate, Tioconazole, Tribromsalan, Triclabendazolum, Zafirlukast	NF-kB	anticancer	[224]
Metformin	TGF-B	For numerous diseases in which TGF-β1 hyperfunction is indicated	[225]
Fresolimumab (GC1008): Monoclonal antibodies against TGF-β	TGF-B	anticancer	[226]
lanreotide, romidepsin, ,pasireotide	TGF-B	anticancer	[227]
Rituximab	PI3K-Akt	Rituximab stops the PI3K-Akt pathway in B-NHL cell lines and sensitizes the drug-resistant tumor cells to apoptosis	[228]
Gefitinib	PI3K-Akt	Gefitinib overcome acquired drug resistance by regulating the PI3K/AKT pathway in non-small cell lung cancer	[229]
Anlotinib	PI3K-Akt	Anlotinib overcomes multiple drug resistant of the colorectal cancer cells via inactivating PI3K/AKT pathway	[230]
Sorafenib	IFN signaling	Sorafenib administration leads to the significant down modulation of IFN-γR1 in Renal cell carcinoma	[231]

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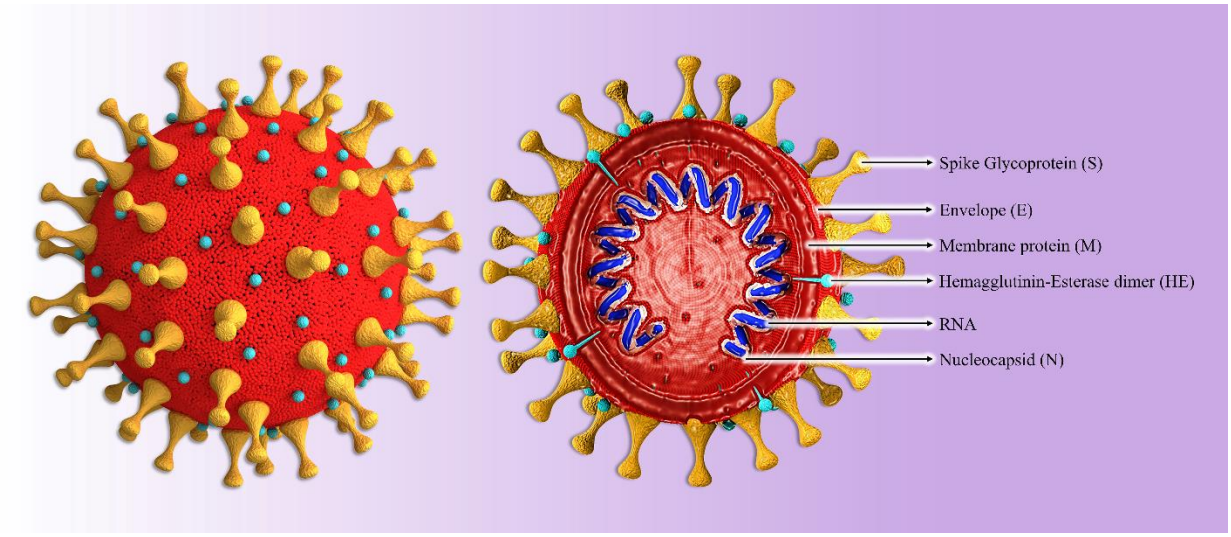

Figure 1: The structure of a typical SARS-CoV-2. The presence of viral S protein gives a crown-like shape to the virion

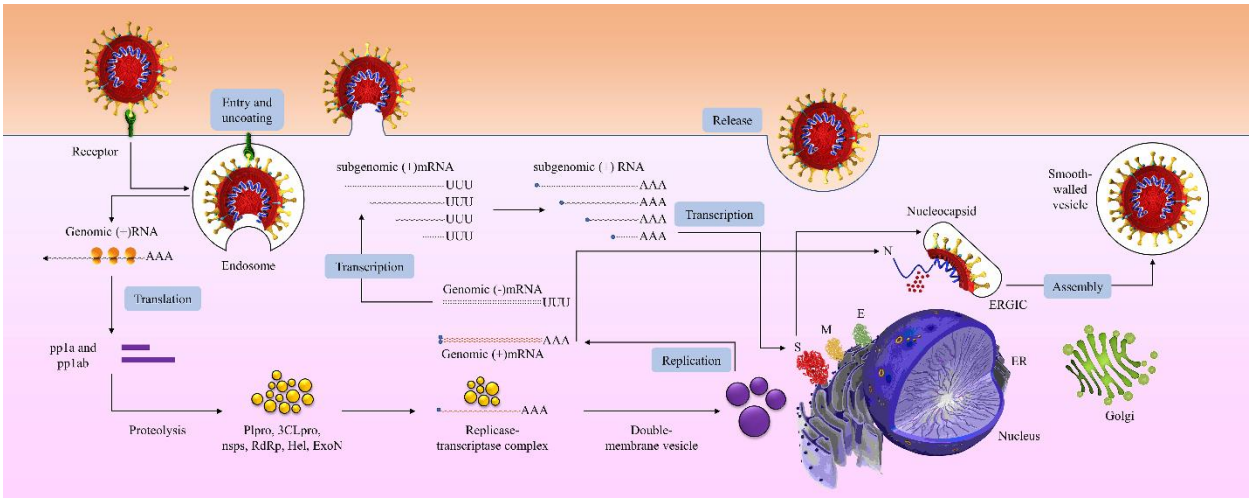

Figure 2: The replication and transcription of SARS-CoV-2. The life cycle of virus is initiated when a virion binds to its related receptor and this event is followed by entry to the hosts cell and uncoating, translation of replicase gene and yielding of pp1a and pp1ab polyprotein. After the production of viral structural proteins such as S, M, and E, the genomic RNA encapsulated by N protein budding into the ERGIC which finally gives rise to the releasing of complete virion from the host cell.

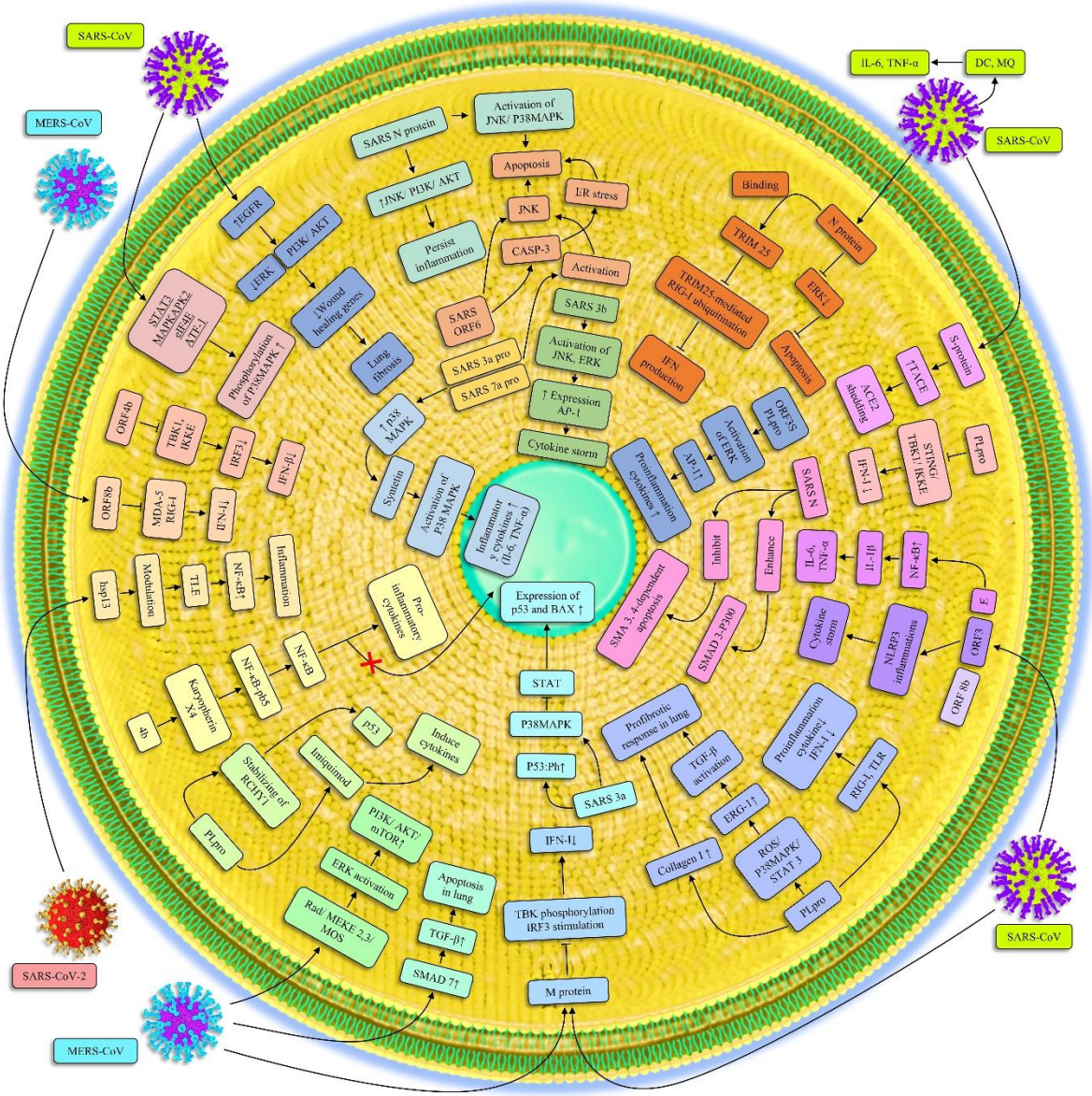

Figure 3: The cellular signaling pathways altered upon coronavirus infection. Once a coronavirus infects its host cell, several cellular signaling pathways are recruited to facilitate the replication of virus. Despite of this recruitment, the activation of such signaling pathways induce inflammation in the host.