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Abstract:

The COVID-19 pandemic has been the focus of research the past two years. The major breakthrough was made by discovering pathways related to SARS-CoV-2 infection through cellular interaction by angiotensin-converting enzyme ACE2 and cytokine storm. The presence of ACE2 in lungs, intestines, cardiovascular tissues, brain, kidneys, liver, and eyes shows that SARS-CoV-2 may have targeted these organs to further activate intracellular signalling pathways that lead to cytokine release syndrome. It has also been reported that SARS-CoV-2 can hijack coatomer protein-I (COPI) for S protein retrograde trafficking to the endoplasmic reticulum-Golgi intermediate compartment (ERGIC), which, in turn, acts as the assembly site for viral progeny. In infected cells, the newly synthesized S protein in endoplasmic reticulum (ER) is transported first to the Golgi body, and then from the Golgi body to the ERGIC compartment resulting in the formation of specific motif on C-terminal end. This review summarizes major events of SARS-CoV-2 infection route, immune response following host-cell infection as an important factor for disease outcome, as well as comorbidity issues of various tissues and organs arising due to COVID-19. Investigations on alterations of host-cell machinery and viral interactions with multiple intracellular signaling pathways could represent a major factor in more effective disease management.

Keywords: SARS-CoV-2, signaling pathways, ACE2, signalomes, pathway interactions

1. Introduction

SARS-CoV-2 (severe acute respiratory syndrome-coronavirus-2) is a highly transmissible and lethal coronavirus that first surfaced late in 2019. It sparked the pandemic of coronavirus disease 2019 (COVID-19), an acute respiratory disease that presents a threat to worldwide public health. Since 2019, the COVID-19 pandemic has been in the spotlight for intensive research to identify signaling pathways for SARS-CoV-2 infection and understand the impact of COVID-19 associated comorbidity [1].

Signalosomes as an example of molecular self-assembly and self-organization are a large supramolecular protein complex that can cluster or oligomerize and play a role in infectivity or serve as a therapeutic target. The COVID-19 signalosome is critical for both the understanding

of infection and immune evasion. SARS-CoV-2 shares many characteristics with other coronaviruses, primarily in terms of genome composition, protein structure, and intracellular processes, which can result in moderate (or even asymptomatic) to severe infectious diseases. Although the mechanisms governing COVID-19 development are not completely understood, recent research suggests that SARS-CoV-2 behaves similarly to other coronaviruses. Uncovering the signaling pathways that may be altered by SARS-CoV-2 infection at the molecular and cellular levels is critical for a better understanding of the genesis and infection of SARS-CoV-2 [2]. This would include cellular interaction by angiotensin-converting enzyme 2 (ACE2) [3–8] and cytokine storm [9–11]. Moreover, it has been reported that SARS-CoV-2 triggers Golgi fragmentation via downregulation of the Golgi reassembly-stacking protein of 55 kD (GRASP55) to facilitate viral trafficking [12]. On the other hand, given the importance of the Raf/MEK/ERK signaling pathway in the pathogenesis of numerous viruses, it is likely that stimulation of this pathway by SARS-CoV-2 plays a key role in virus survival. Inhibitors of the Raf/MEK/ERK signaling cascade might be promising antiviral targets for the treatment of COVID-19 [13].

Several studies have looked at lipidomic profiling in COVID-19 patients. Although the analytical methodologies utilized and patient demographics vary among these studies, certain similar findings have been reported, notably with regards to blood cholesterol and lipoproteins. In individuals with COVID-19, serum triglycerides and very-low-density lipoprotein (VLDL) levels are much higher, although high-density lipoprotein (HDL) and low-density lipoprotein (LDL) levels remain significantly lower compared to age- and sex-matched healthy controls [14–17]. Comparison of COVID-19 patients to healthy controls by metabolomic and transcriptome profiling showed a change in fatty acid oxidation, which might imply a metabolic transition to feed viral replication [14,18]. Most studies have shown that following recovery, HDL and LDL levels reverted to baseline. However, other research suggested that changes in lipid metabolism continue even after COVID-19 recovery [19,20].

Given the presence of ACE2 in lungs, intestines, cardiovascular tissues, brain, kidneys, liver, and eyes, SARS-CoV-2 may have targeted these organs to further activate intracellular signaling pathways that lead to cytokine release syndrome (CRS). As a result, COVID-19 patients have experienced symptoms linked to all these systems [3,21]. A coherent cellular and molecular

route for SARS-CoV-2 infection has been presented with the goal of combining early results [22]. In this proposed pathway, SARS-CoV-2 membrane fusion and cytoplasmic entry via ACE2 and transmembrane serine protease-2 (TMPRSS2)-expressing respiratory epithelial cells induce an initial immune response characterized by inflammatory cytokine production and a weak interferon response, particularly in interferon (IFN)-λ dependent epithelial defense [22]. However, as suggested by literature data, COVID-19 patients are characterized with heterogeneous pattern of IFN response. Jackson et al (2020) evaluated the expression levels of IFN in twenty-six critically ill SARS-CoV-2 patients treated with standard of care therapy. During the viral replication phase (day 8-10 of the infection), a peak in IFN-α2 expression was observed that decreased over time, but still until detectable level. On the contrary, 19% of the patients were characterized with sustained abrogation of IFN-I production. Patients without IFN-α production had a poorer disease outcome requiring invasive ventilation. In IFN-negative patient group, viral load was higher, while IFN-β and –λ were also not detected. Controversial results of IFN response in COVID-19 patients suggest that patient screening for IFN production could be an important approach for therapeutic interventions of COVID-19 patients Non-classic pathogenic T-cell differentiation and pro-inflammatory intermediate monocyte differentiation contribute to a skewed inflammatory profile, which is mediated by membrane-bound immune receptor subtypes (e.g., human immunoglobulin receptor II A (FcRIIA)) and downstream signaling pathways (e.g., nuclear factor-kappa B (NF-κB), p65 and p38 mitogen activated protein kinase (MAPK)), followed by chemotactic infiltration of monocyte-derived macrophages and neutrophils into lung tissue. Inflammatory cytokine release and delayed neutrophil apoptosis contribute to pulmonary thrombosis and cytokine storm. These mechanisms are consistent with clinical markers observed in COVID-19 patients, such as high tumor necrosis factor (TNF)-/IL-6 expression, elevated neutrophil-to-lymphocyte ratio (NLR), diffuse alveolar damage via cell apoptosis in respiratory epithelia and vascular endothelia, elevated lactate dehydrogenase (LDH) and C-reactive protein (CRP), high production of neutrophil extracellular traps (NETs), low platelet count, and thrombosis [22]. Although key sections are likely to be updated as new discoveries emerge, the suggested pathway offers a number of possible treatment strategies. Additional therapies aim to reduce inflammatory signaling and damage, as well as to target molecular mediators of the maladaptive COVID-19 immune response (e.g., IL-6, TNF-, IL-17, JAK, and CDK9) [22].

It is widely known that pre-existing comorbid illnesses such as hypertension, diabetes, obesity, cardiovascular diseases (CVDs), chronic kidney diseases (CKDs), and chronic obstructive pulmonary disease (COPD) are linked to greater COVID-19 severity and mortality. The higher mortality from COVID-19 is attributable to the lack of a gold standard therapy and, more critically, not having a full understanding of how comorbid illnesses and COVID-19 interact at the molecular level, allowing tailored management methods to be implemented [23]. Barh et al. used multi-omics data sets and a bioinformatics approach to identify the pathway crosstalk between COVID-19 and diabetes, hypertension, CVDs, and CKDs [23]. On the other hand, limited evidence has shown that autoimmunity may be involved in patients with COVID-19 [24]. According to Sacchi et al., COVID-19 patients with a de novo autoimmune response had the poorest acute illness prognosis and outcome [24]. Their findings support the concept that SARS-CoV-2 infections are associated with autoimmune markers. However, research is still needed to define the pathway-pathway interaction in mental health and neurological and ophthalmic diseases.

Furthermore, SARS-CoV-2 signaling has been found to play a role in cell proliferation and death. The Coronavirus Research Group at the University of California isolated 26 SARS-CoV-2 proteins to create a network of virus-host protein-protein interactions [25]. They detected 332 human proteins targeted by SARS-CoV-2, as well as 69 FDA-approved drugs which might be repurposed and evaluated in clinical trials for the disruption of the virus-host protein-protein interactions. Twenty-three of the 46 proteins evaluated in clinical trials on cancer were annotated [25]. Cancer cells and pathogens employ similar molecular pathways to control apoptosis and evade host defense. Infection with distinct RNA or DNA viruses has been associated with oncogenesis by activating cellular oncogenes or decreasing tumor suppressors, providing evidence for shared viral targets and cancer inducers [25]. As a result, system-wide integration of protein–protein interactions that drive viral pathogenicity and cancer has the potential to discover important factors that increase the dysregulation of cellular mechanisms [25].

In this review we present the importance of COVID-19 signalosome pathways in terms of infectivity, and pathway-pathway interactions. Moreover, we describe the impact of the COVID-19 signalome on COVID-19 associated comorbidity.

2. Pathways for systemic infection of SARS-CoV-2

2.1. ACE2-mediated infection

SARS-CoV-2 is mainly composed of four structural proteins, including spike glycoprotein (S), membrane (M), envelope (E) and nucleocapsid (N) proteins. Each protein has its distinct role in the viral replication process [26]. Additionally, SARS-CoV-2 presents biological features that are mainly involved in the interaction with ACE2 [2], which is widely expressed in the human body, including renal, lymphoid and cardiovascular tissues as well as the gastrointestinal (duodenum, jejunum, ileum, cecum and colon), respiratory and central nervous systems [3]. Based on different studies, it has been confirmed that ACE2 serves as a functional receptor for SARS-CoV-2 [2] (**Figure 1**). The cellular entry of SARS-CoV-2 is mediated by high affinity binding of the S protein to ACE2 and the processing of TMPRSS2 on the host cell surface allowing S protein priming [27].

2.2. ER- and Golgi-mediated trafficking

SARS-CoV-2 can hijack coatomer protein-I (COPI) for S protein retrograde trafficking to the endoplasmic reticulum-Golgi intermediate compartment (ERGIC) [28]. The ERGIC acts as the progeny assembly site. In infected cells, the newly synthesized S protein in endoplasmic reticulum (ER) is transported first to the Golgi body, and then from the Golgi body to the ERGIC compartment. The resulting retrograde trafficking of the post-translationally modified S protein from the Golgi body to the ERGIC may include a cytosolic dibasic motif, Lys-x-His, where x is any amino acid [28]. Such C-terminal dibasic motifs and variants such as K-x-K-x-x are widely reported in the cytosolic tail of host membrane proteins. That is why the β-coronavirus S protein demonstrates molecular mimicry of dibasic trafficking motifs [28].
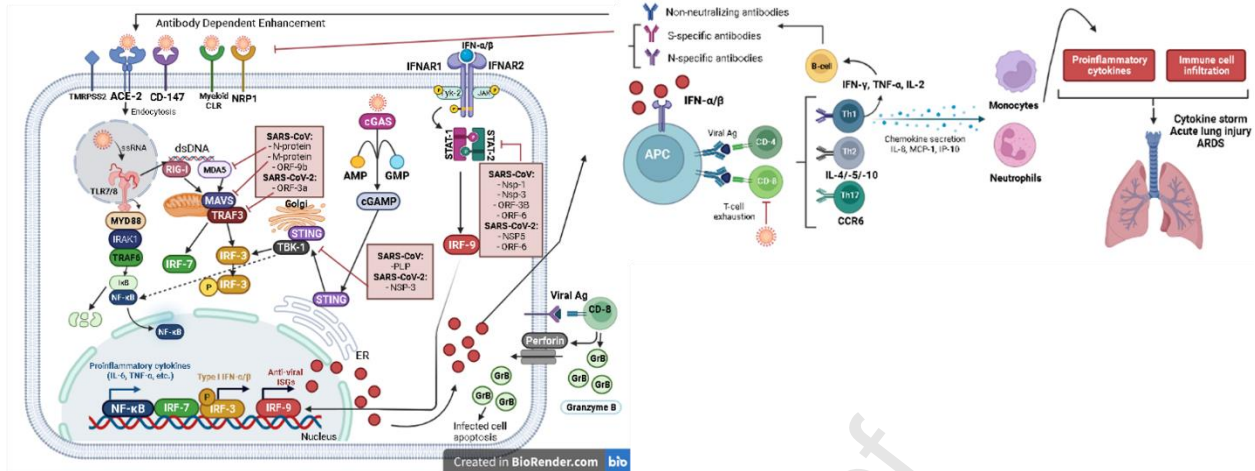
Figure 1: Overview of the SARS-CoV-2 infection mechanism and the post-infection host immune responses. The diagram illustrates the role of TMPRSS2, ACE-2, and CD147 during SARS CoV-2 infection, innate and adaptive immunity, and SARS-CoV-2 viral entry via receptors. Host immune defense begins early with the initiation of PRR signaling (TLRs, RLRs, CLRs and cGAS-STING) leading to activation of type I IFN along with proinflammatory cytokines [29]. The figure has been created using BioRender (www.biorender.com)

2.3. SARS-CoV-2 survival pathways

The Rapidly Accelerated Fibrosarcoma / Mitogen-activated protein kinase / Extracellular signal-regulated kinase (Raf/MEK/ERK) signaling pathway is one of the most well-known signal transduction pathways [30]. It shows an important impact on a wide variety of cellular functions such as cell proliferation, cell cycle arrest, and apoptosis. A chain of proteins in the cell transmits the signal from a surface cell receptor to the cellular DNA [30]. Previously, related to the SARS epidemic caused by SARS-CoV, it was demonstrated that the transiently expressed SARS-CoV S protein played an important role in virus-stimulated cyclooxygenase-2 (COX-2) expression [13]. COX-2 is a prostaglandin synthetase involved in inflammation, which is highly regulated by different factors, including cytokines. It has been shown that the SARS-CoV S protein induces calcium-dependent protein kinase C Alpha (PKCa) upstream, which in turn modulates the downstream Raf/MEK/ERK pathway [13]. A possible role of the Raf/MEK/ERK pathway in viral survival has been recently suggested for SARS-CoV-2 [13].

2.4 Immune escape pathways

The antiviral IFN system acts as the first line of defense against viral replication and dissemination. Surprisingly, IFN responses appear to be weak during the SARS-CoV-2 infection [31], indicating that the antiviral system is effectively counteracted by SARS-CoV-2 [32]. COVID-19 pathophysiology and severity are likely exacerbated by a lack of IFN responses, which allows productive viral replication [32–34].

The antiviral IFN system based on type I IFNs (particularly IFN-α and IFN-β) and type III IFNs (IFN-λ) plays an important role in host defense against viral infections [35,36]. Minimal production of antiviral IFNs in cultured cells, animal models, and in patients with severe COVID-19 clearly demonstrate the extremely effective suppression of innate immune responses by the virus [32,37]. Given the potent, diverse antiviral and immunoregulatory activities of type I and III IFNs, SARS-CoV-2 inhibition of IFN response would not only directly facilitate the evasion of multifaced antiviral actions of numerous interferon-stimulated genes (ISGs) but affect numerous innate and adaptive immune responses. For example, natural killer (NK) cells, dendritic cells (DCs), macrophages, and lymphocytes contribute to cell-mediated release and clearance of viruses [38–40].

SARS-CoV-2 appears to be equipped with various IFN antagonists to interfere at multiple levels of the host antiviral IFN responses, which may contribute to its strong adaptation in the human population as demonstrated during the pandemic [41]. A number of putative IFN antagonists have been proposed since the beginning of the pandemic, each with a different mode of action. However, further studies are required to offer a clearer picture of the antagonism between SARS-CoV-2 and IFNs [41].

2.5. Cytokine storm

Induction of inflammatory cytokines by the SARS-CoV-2 S- protein, which is associated with epithelial damage and organ injuries may contribute to the cytokine storm in COVID-19 patients. The SARS-CoV-2 open reading frame 3a (ORF3a) also participates in induction of the cytokine storm. However, when concentrations of T helper (Th)17 cells, perforins, and granulysin-expressing cluster of differentiation 8 T-cell (CD8 T) cells are enhanced, it will contribute to

hyperinflammation. Moreover, host Th17 responses are major contributors to cytokine storms [42]. Animal studies have shown that TNF-α and IFN-γ together induce a SARS-CoV-2-like cytokine storm in mice. The induced storm can be reversed using PANoptosis inhibitors [42].

2.6. Membrane lipids in SARS-CoV-2 cell entrance and infectivity

The lipid composition of cell membranes plays a role in viral cell entry, which can be attained by mediating fusion or affecting receptor conformation [43]. Several classes of lipid mediators can regulate the host immune response to viral infection. Examples of such mediators include eicosanoids and sphingolipids [43]. It has also been reported that the SARS-CoV-2 S protein can bind cholesterol in HDL particles, and that uptake of HDL by scavenger receptor class B type 1 (SR-B1) can occur. It can facilitate viral entry into cells, which co-express the ACE2 receptor [43].

The S protein in the envelope of SARS-CoV-2, responsible for binding and fusion to host cell membranes, is subjected to lipid modifications through the sequential action of zinc finger DHHC-type palmitoyltransferase 20 (ZDHHC20) and 9 S-acyltransferases [44]. Acetylation increases fusion capacity of viral particles and improves viral infectivity [45].

2.7. Sharing pathways with other viruses, bacteria, and protozoan parasites

Previous experimental and observational studies on inter-human viral infection have indicated a significant role of aerosols in the infection of many respiratory viruses, including influenza virus, SARS-CoV, SARS-CoV-2, and Middle East respiratory syndrome coronavirus (MERS-CoV) [46]. The most common symptoms of COVID-19 are similar to those seen in the case of influenza virus infection including shortness of breath, fever, running nose in addition to other symptoms like loss of taste and smell, nausea, vomiting, and diarrhea [47]. Furthermore, SARS-CoV-2 immunization has been demonstrated to generate heterologous immunity against bacterial peptides. These findings suggest a mechanism for heterologous T-cell immunity against common bacterial infections and SARS-CoV-2, which might explain the wide range of COVID-19 clinical outcomes from asymptomatic to severe forms [48]. In the case of protozoan parasites, SARS-CoV-2 has been shown to share pathways with organisms causing toxoplasmosis, leishmaniasis, and malaria [49].

3. Signaling pathways deregulated in host tissues and organs

3.1. Lung

It is widely recognized that COVID-19 development is driven by an inflammatory state produced by hyperactivation of the immune system [50]. As a result, illness severity in individuals is caused not only by the viral infection, but also by the diversity of the host's innate and adaptive immune responses, which can result in a broad range of clinical outcomes, from asymptomatic to severe disease, multiple organ failure, and death [50]. A combination of cytopathic impact, prolonged inflammation, and immune system activation causes lung tissue damage and dyspnea [21]. Fassan et al. examined transcriptome data from post-mortem lung tissues and discovered a highly disturbed inflammatory pathway [51]. Genes specifically activating endothelial cells and TNF-family signaling pathways were downregulated in samples from COVID-19 patients compared to controls [51]. Interferon-stimulated genes (ISGs), monocyte/macrophage activation-associated genes, the complement system, and Cathepsin C were all upregulated in specimens from COVID-19 patients [51]. High levels of IFN in patients with severe COVID-19 might theoretically increase inflammation and tissue damage [52,53]. Recent research discovered low CD169/Siglec1 and high CD163 expression in circulating monocytes in patients with severe COVID-19, where the early stages of COVID-19 were characterized by enrichment of CD169/Siglec1+ monocytes in the peripheral blood [54]. Local CD163+ monocyte enrichment is related to anti-inflammatory macrophage actions [55], whereas CD169/Siglec1+ monocyte abundance implies IFN1 pathway activation [56]. IFN1 was identified as the primary driver of the dysregulated inflammatory and immunological milieu found in the lungs of COVID-19 patients [53].

3.2. Heart

COVID-19 survivors have been reported to suffer late-onset cardiovascular sequelae, including myocarditis-like alterations revealed by cardiovascular magnetic resonance imaging [57-59]. The long-term consequences of COVID-19 myocarditis, as well as the processes and extent of cardiac injury are yet unknown [57-59]. Emerging data show that autophagy plays an important role in SARS-CoV-2 infections [60]. SARS-CoV-2 has been found to casually modulate cellular metabolism to reduce autophagy for support of replication and propagation, similar to MERS-CoV [60,61]. SARS-CoV-2 has been found to reduce autophagy by interacting with Beclin1 to suppress antiviral innate immunity and increase viral escape and replication [61]. Many human

heart disorders, including ischemia–reperfusion damage, myocardial infarction, cardiac hypertrophy, and heart failure, have been associated with Beclin1 deregulation [62]. Survivin, the smallest member of the family of apoptosis inhibitors, has been demonstrated to interact with Beclin1 [63]. Survivin overexpression is associated with an increase in critical components of the autophagy process, particularly Beclin1 [64]. There is evidence of an association between IFN-γ and Beclin1 activation *in vitro* and *in vivo* [65]. Notably, IFN-γ has been identified as an independent risk factor for death in individuals with moderate to severe COVID-19. It has been demonstrated that IFN-γ is expressed at much higher levels in COVID-19 patients compared to controls, and that this expression increases over time in severely ill COVID-19 patients [66]. According to Mormille, SARS-CoV-2 causes IFN-γ upregulation which enhances Beclin1 expression and improves SARS-CoV-2 cell entry and infectivity [67].

3.3. Kidney

A link between SARS-CoV-2 infection and acute kidney injury (AKI) has been documented in more than one-third of hospitalized COVID-19 patients [68]. According to both native and post-mortem renal investigations, acute tubular damage is the histological characteristic of COVID-19 kidney disease [69]. Alexander et al. discovered higher levels of apoptosis in the kidneys of COVID-19 and Sepsis-AKI (S-AKI) patients [70]. The observed upregulation of the ceramide pathway in the COVID-19 AKI cohort, together with the lower oxidative phosphorylation signals, suggest that ceramide-induced apoptosis via mitochondrial disruption may play a role in tubular cell death [71,72]. The increased ceramide pathway in COVID-19 AKI supports the involvement of lipid dysregulation in severe cases of COVID-19, as previously proposed. Necroptosis, an immunogenic cell death process that may destroy virus-infected cells as well as activate both innate and adaptive immune responses to limit viral replication, was likewise more severe in the kidneys of COVID-19 patients [73]. Furthermore, the molecular signs of inflammation and immunological activation detected in the kidneys of COVID-19 patients point to a systemic antiviral response characterized by macrophage and T-cell–rich inflammation and type II IFN production, as revealed by blood-based tests [74]. On the other hand, SARS-CoV-2 specific CD4+ T cells directed against the S protein have been detected in patients with severe COVID-19 and may account for the CD4+ T cells found in the tubulointerstitial compartment of the kidneys [75]. The molecular pathways studied at both the genomic and proteomic levels

indicated that inflammation, like S-AKI, is the primary cause of the kidney damage found in COVID-19 patients [69].

3.4 Liver

Another SARS-CoV-2 receptor, neuropilin-1 (NRP-1) has recently been shown to be expressed on the surface of host cells during infection [76,77]. NRP-1 belongs to the NRP protein family, which also contains NRP-2. NRP-1 was originally discovered in the central nervous system but has since then been identified in numerous cell types in the heart, lung, pancreas, skeletal muscle, and liver. NRP-1 is found in liver-resident cells, particularly nonparenchymal cells such as sinusoidal endothelial cells (LSECs) and hepatic stellate cells (HSC). NRP-1 has recently been discovered as a receptor that facilitates SARS-CoV-2 infection [77]. It may alter the state of liver disease in COVID-19 patients since it is expressed in liver cells [77]. The durability and severity of COVID-19-induced liver damage appear to differ. In most cases, liver function quickly returns to normal following viral infection, but individuals with severe illness may suffer long-lasting hepatic damage [78,79]. According to this observation, increasing severity of COVID-19 disease is associated with decreased hepatic function [21,80]. Recently, microvesicular steatosis as well as lobular and portal activity were discovered in the post-mortem examination of a COVID-19 patient [81]. ACE2 expression in cholangiocytes has also been hypothesized as a potential cause of liver damage. NRP-1 expression in LSECs and HSCs may thereby increase liver damage caused by SARS-CoV-2 infection [82].

3.5 Brain

Critically ill COVID-19 patients show increased levels of pro-inflammatory mediators and cytokines, indicating a "cytokine storm syndrome" [83]. The NF-κB pathway is upregulated in the severe/critical pathogenesis of the COVID-19 phenotype [84]. The NF-κB complex is found in both neurons and glia cells, and it has been linked to neurodegenerative disorders [85,86]. The NF-κB signaling pathway is regarded as a proinflammatory route, owing to its influence on transcription of several genes implicated in inflammation [87]. Inhibition of the NF-κB pathway boosted survival rates in mice infected with SARS-CoV, indicating that activation of the NF-κB signaling system contributes significantly to the inflammation caused by SARS-CoV infection [88]. The SARS-CoV S protein stimulates the NF-κB pathway in infected mononuclear cells. The cytokine response triggered by Toll-like receptor (TLR) activation was suppressed by NF-

κB inhibition via protein kinase C-dependent mechanism [89]. As a SARS-CoV-2 binding protein, ACE2 can convert Angiotensin II, which can then function as a proinflammatory cytokine via the angiotensin-1-receptor (AT1R). AT1R can activate the NF-κB pathway [90] culminating in the creation of epidermal growth factor receptor (EGFR) ligands and TNF-α, which further activates NF-κB and propagates a "cytokine storm" [83,84]. According to emerging evidence, SARS-CoV-2 causes a variety of unanticipated consequences on neurological function, resulting in symptoms such as headache, decreased consciousness, anosmia, dysgeusia, stroke, encephalopathy, myelitis, neuritic pain, myalgia, and rhabdomyolysis [91]. COVID-19 shares a neuropathogenesis profile with other viral diseases that can activate the NF-κB pathway, such as MERS, herpes viruses, varicella, and cytomegalovirus (CMV) [92].

3.6. Eye

SARS-CoV-2 enters host cells using ACE2 as a receptor. Wang et al. discovered Basigin (BSG), also known as CD147, as a novel receptor for SARS-CoV-2 entry into host cells [93]. Although the cysteine proteases cathepsin B and L (CTSB/CTSL) can also execute this role to a lesser extent, TMPRSS2 is a major participant in cleaving and activating the SARS-COV-2 S protein for viral entry [27]. Determination of which cell types are susceptible to SARS-CoV-2 infection can be carried out by analyzing the expression of the above-mentioned genes in different organs. Other mechanisms of infection in addition to respiratory droplets have emerged. One alternative is the ocular pathway, which was recently discovered [93,94]. It has been suggested that ACE2 and TMPRSS2 may play roles in SARS-CoV-2 entry in ocular cells, where tissues in the cornea also express ACE2 and superficial conjunctival cells co-express ACE2 and TMPRSS2 [95]. The presence of interferon receptors (IFNAR1 and IFNAR2) in corneal conjunctival and endothelial cells suggests a possible association between these cell types and infection. During SARS-CoV infection, the virus suppresses the expression of transcription factors IRF3 and IRF7, which are essential for IFN induction [96]. The model of infection of conjunctival cells by viruses such as SARS-CoV-2 has been postulated and interaction between conjunctival and endothelial cells has been observed by looking at the expression of interferon regulators (IRFs) and receptors. IRFs are activated after viral infections. These IRFs (IRF7, IRF3, DDX3, and RIOK3) exhibit high expression in conjunctival cells based on basal gene expression in non-infected corneal cells

[97]. IFNs generated by infected cell types may interface with endothelial cell types that express IFNARs such as IFNAR1 and IFNAR2 after infection [97]. STAT2 and IRF9 are also expressed at high levels in endothelial cells, which may trigger the release of cytokines such as IL-6, as seen by the high level of IL-6 expression in endothelial cells [97]. It has been demonstrated that IL-6 activates STAT3 transcription factors and the NF-κB pathway [98]. ACE2, on the other hand, has been demonstrated to inhibit STAT3 expression during lung inflammation [97]. Conjunctival cells express TMPRSS2 and ACE2, indicating that conjunctival sacs might be the entrance site for SARS-COV-2. CTSB and CTSL, on the other hand, were expressed in ACE2+ corneal epithelial cell types, indicating that SARS-CoV-2 might infect a specific population of epithelial cells in the cornea. SRY-b/ox transcription factor 13 (SOX13) was shown to be one of the intriguing gene candidates among the genes that were strongly co-expressed with ACE2 and TMPRSS2 [97]. SOX13 target genes such as PR domain zinc finger protein 1 (PRDM1) and phospholipid scramblase 2 (PLSCR2), affect IFN signaling pathways and generates high expression of IL-6 in endothelial cell types, which was detected while examining the microenvironment of corneal cell types, representing one of the cytokines that is highly expressed in patients with severe COVID-19 [97].

3.7. Skin

SARS-CoV-2 infection has been associated with the activation of cutaneous and systemic immune responses in different skin manifestations [99]. The type I IFN family, which contains three secreted cytokines IFN-α, IFN-β, and IFN-γ, is a major component of the immune response to numerous infections including SARS-CoV-2. These type I IFNs are generated in response to viral nucleotide sensing via Toll-like receptors (TLRs). Type I IFNs are released and detected by other cells in the tissue environment [99]. However, when type I IFNs are triggered improperly in response to self-antigens or nucleic acid accumulation, this same mechanism can contribute to the development of autoimmune illnesses [100]. IFN response if one of the important factors in COVID-19 management, where early type I IFN response in some patients results in infection control and mild disease course. Therefore, severe COVID-19 has been associated with low type I IFN levels in the blood as well as reduced white blood cell expression of type I IFN–stimulated genes [101]. One of the signs of effective IFN response in COVID-19 patients is observed through skin manifestation of so-called "COVID toes". This appearance is histologically

characterized with epidermis edema and lymphocyte infiltration in perivascular and perieccrine regions, followed by formation of microthrombi in the blood vessels. The acral areas appear with red-purple discoloration and blistering. Similar changes are also observed in autoimmune disorders, such as familiar chilblain lupus, an interferonopathy correlated to increased IFN type I production. Appearance of the mentioned skin manifestation in COVID-19 patients suggests the presence and secretion of type I IFN that indicates mild COVID-19 course and efficient SARS-CoV-2 clearance . Other studies have demonstrated that defects in the type I IFN pathway, whether caused by mutations or the production of autoantibodies, predispose individuals to severe COVID-19 [102]. Surprisingly, it was discovered that 135 (or 14.4%) of 937 patients with severe COVID-19 developed autoantibodies against type I IFN, compared to 0% of patients with moderate or asymptomatic COVID-19 and 0.3% of healthy controls [102]. As a result, it is possible that individuals with pre-existing autoantibodies are predisposed to acquiring severe COVID-19. **Figure 2** schematically summarizes signaling pathways, which are deregulated in host tissues and organs and shows intricate complexity of the associated processes.
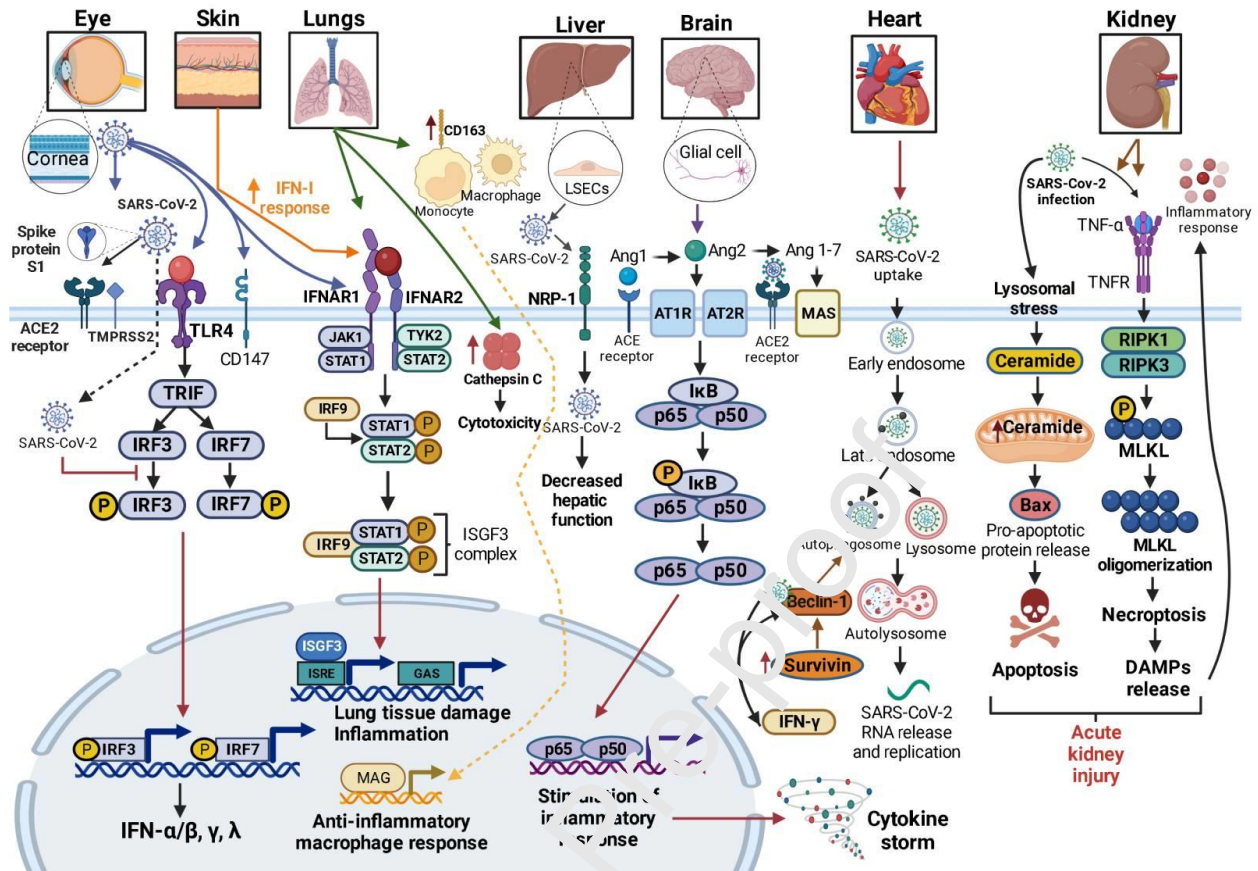
Figure 2: Summary of signaling pathways deregulated in host tissues and organs. The figure has been created using BioRender (www.biorender.com)

4. Pathway-pathway interactions in COVID-19 associated comorbidity and long-term consequences

4.1. Diabetes

Diabetes is considered an independent risk factor for COVID-19. Its macro- and microvascular complications affect the quality of life, and it is associated with several other infections. Many studies have demonstrated the high prevalence of diabetics who also suffered from COVID-19 [103–107]. According to an integrated analysis, people with severe COVID-19 show a severely compromised type I IFN response and low blood levels of IFN activity, which indicates a high blood viral load, and a compromised inflammatory response [37]. Additionally, it has been revealed that the TLR3 and IRF7 B cell immunity was associated with inborn errors in type I

IFN immunity [34]. Furthermore, independent predictors of the severity of COVID-19 include blood levels of IL-6 and LDH [108]. In individuals with diabetes mellitus, the damage caused by IL-6 to DNA, proteins, lipids, and other components of the body might accelerate the progression of COVID-19. Pro-inflammatory cytokines with a Th1 cell signature are also known to worsen insulin resistance in obese people [109]. Acute respiratory viral infections have been demonstrated to enhance IFN production and to promote muscular insulin resistance in humans. This results in compensatory hyperinsulinemia, which maintains euglycemia and stimulates antiviral CD8+ T cell responses [110]. There is some evidence linking ACE2 to the control of hyperglycemia. For instance, it has been discovered that high-fat diets can cause pancreatic cell dysfunction, but ACE2-knockout animals are more vulnerable than wild-type mice to this condition. Additionally, SARS-CoV-2 infection can result in hyperglycemia in patients who do not already have diabetes mellitus [111,112].

4.2. Thrombosis and vascular injury

Abnormal clotting, thrombosis, microvascular lesions, and preeclampsia are clear complications that patients with COVID-19 are facing, leading to abnormal vascular problems [113]. Neutrophils are the main cell type recruited to the lungs during SARS-CoV-2 infection, which has been confirmed in several studies demonstrating their association with thrombosis and microvascular injury [113]. There are a number of proinflammatory cytokines and chemokines that can be differently expressed in the cytokine-cytokine receptor and chemokine signaling pathways [114]. Down-regulated chemokine ligand 14 (CXCL14) promotes the ability of epithelial cells to produce chemokines, which will lead to additional neutrophil recruitment. Up-regulated CXCL1, CXCL2, CXLC3, CXCL5, and CXCL8 have a prominent role associated with the recruitment of neutrophils to the lungs [114]. Additionally, type I IFN responses are recognized to be essential for a coordinated and effective immune response to viral infections [115]. The only ISG that was up-regulated during the type I IFN response in lung epithelial cells infected with SARS-CoV-2 was IL-6 [114], which is similarly crucial for neutrophil recruitment, function, and survival. An increased number of neutrophils that generate superoxide at a higher rate than typical neutrophils as a result of IL-6 upregulation, may result in tissue damage [113]. Similarly, neutrophil extracellular trap (NET) formation has been shown to be crucial for the pathophysiology of pulmonary lung diseases like COPD or acute lung damage. Several

important cytokines that are crucial for NET regulation and synthesis, such as CCL20, IL-6, TNF, CXCL8, and IL-1, were up-regulated [116,117]. Several studies have demonstrated that pulmonary microvascular thrombosis may be responsible for the high mortality rate in patients with SARS-CoV-2 and acute respiratory distress syndrome. There are reports that thrombosis is commonly found in small vessels, lungs and even some extrapulmonary organs [118,119]. Platelets are one of the key factors in thrombosis. It is interesting to note that in samples from COVID-19 patients, a considerable up-regulation of colony stimulating factor 2 (CSF2), CSF3, IL-6, and IL-1 occurred. These cytokines are known to play a role in platelet formation and megakaryocytic activity [120-122].

4.3. Hypertension and cardiovascular diseases

Hypertension has been reported in surveys in several countries as the most common comorbidity among individuals infected with SARS-CoV-2. Associated with heart failure and arrhythmia are some of the diseases of the cardiovascular system that can generate several complications in the course of SARS-CoV-2 infection [123-125]. Hypertension has been shown to be associated with a significantly higher risk of respiratory infection, making it a strong indicator of the severity of COVID-19. Hyperinflammation or "cytokine storms" are caused by SARS-CoV-2 infection, which stimulates both innate and adaptive immune responses and causes the production of proinflammatory substances. Type I IFN, which is essential for preventing viral infections, is decreased in patients with severe COVID-19 due to a large reduction in ISGs [37]. A decline in immune cells such as CD4+ T cells, CD8+ T cells, NK cells, and B cells induces lymphopenia [126]. IL-1, IL-6, IL-17, and TNF-α are among the cytokines with rapidly enhanced levels in the blood in the majority of individuals with severe COVID-19; this phenomenon is known as the "cytokine storm" [127]. Immune cells that produce cytokines contribute to organ damage and vascular dysfunction. In the inflammatory environment, patients with hypertension have higher levels of circulating monocytes, macrophages, CD8+ T cells, and CD4+ T cells [128]. High blood pressure causes immune cell infiltration and activation in the heart, as well as an immediate cardiac inflammatory response. Additionally, patients with catastrophic outcomes showed significant levels of CD38+ and human leukocyte antigen-DR isotype-positive (HLA-DR+), two essential indicators of CD8+ T-cell activation, as well as programmed cell death protein 1-positive (PD-1+), a hallmark of CD8+ T-cell activation and exhaustion, on CD8+ T

cells after SARS-CoV-2 infection. Immunoglobulins like IgG, IgM and IgA as well as the proportions of SARS-CoV-2-specific IFN+ CD4+ T cells and IFN+ CD8+ cells were all significantly lower in fatal cases, indicating that T cells are crucial for clinical outcomes in COVID-19 patients with hypertension [129].

4.5. Renal diseases

The increase in the hospital mortality rate from COVID-19 is associated with kidney injuries in patients, because, just as the death of epithelial cells is induced by histones, the histones of NETs also induce the death of tubular epithelial cells, which leads to kidney injury [130]. ***In situ*** studies of the viral nucleocapsid protein in post-mortem kidneys demonstrated that SARS-CoV-2 antigens had accumulated in the renal tubules, suggesting that SARS-CoV-2 infects human kidneys directly, inducing AKI and contributing to viral spread in the body [131]. The production of a cytokine storm induces T cell necrosis or death, which results in a decrease in T cells, especially in situations of severe illness, lower levels of circulating CD4 and CD8 T cells, and higher levels of IL-10 and TNF [132]. Because macrophages are crucial, innate immune cells have the ability to detect infections, respond, and produce inflammatory chemicals to eliminate them and aid in tissue healing. SARS-CoV-2 enters macrophages, which then release IL-12 to further activate Th1 cells by presenting viral antigens to CD4+ and Th1 cells. B cells are stimulated to generate antigen-specific antibodies by the activated Th1 cells, and CD8+ and T-killer cells (CD8+ and Tk) are directed against cells carrying viral antigens [133]. CD8+ T cells have an antiviral function and either directly or indirectly cause their cytotoxic effect. T cells activate the NF-κB signaling pathway, which results in the generation of pro-inflammatory cytokines. Following the secretion of chemokines and cytokines such as IL-21, IL-8, TNF-α, IL-6, IL-1β, C-C motif chemokine ligand (CCL)-2, -3, and -5, the cytokine storm occurs, being responsible for multiple organ damage [134]. The cytokine storm may contribute to AKI in COVID-19 patients through interaction with renal resident cells. IL-6 causes renal endothelial cells to secrete pro-inflammatory chemokines and cytokines and increases kidney vascular permeability, which may lead to microcirculatory dysfunction [135]. On the other hand, viral infection causes CD4+ T cells and NK cells to infiltrate into the tubular interstitium and releases pro-inflammatory cytokines, which damages the tubules. If these immune cells are overactive

after entering the infected kidney, it can cause fibrosis, apoptosis, and microvascular changes [136,137].

4.6. Neurological syndromes and mental health

It is evident that after infection by SARS-CoV-2 many patients present neurological symptoms and syndromes [138]. Persistence of multiple symptoms, particularly fatigue, dyspnea, sleep disturbances, and subjective memory complaints, has been reported [139]. The long-term consequences of COVID-19 involve the central and peripheral nervous systems [138-141]. The risk of cerebrovascular events (ischemic stroke and intracranial hemorrhage) is considered high for COVID-19 [142,143]. Multiple organ failure has been identified as the cause of a significant proportion of SARS and COVID-19 deaths. Through the stimulation of glial cells and the ensuing large production of inflammatory molecules including cytokines, chemokines, and other inflammatory signals, a neurotropic virus can induce persistent inflammation and brain injury [144]. The brain-blood barrier (BBB) is then significantly breached as a result of the inflammatory signals that are generated, which activates and amplifies the neuroinflammatory process [144]. It has been demonstrated that SARS-CoV infections cause primary glial cells to release interleukins, including IL-6, IL-12, IL-15, and TNF-α *in vitro* [145]. Additionally, it has been documented that IL-6 is positively correlated with the severity of COVID-2019 symptoms [144].

4.7. Ophthalmic diseases

In a large series of cases with mild COVID-19, 11/127 (8.66%) patients had conjunctivitis, which is the most common ophthalmic manifestation documented in patients with COVID-19 [146]. Many of the characteristics that increase the chance of acquiring COVID-19 also enhance the risk of developing eye conditions including age-related macular degeneration (AMD). The impact of elevated levels of various pro-inflammatory cytokines, including IL-6 and TNF-α receptor 2, on the development of advanced stages of AMD has been investigated [147]. One prospective study of 251 participants aged 60 and older found that the highest quartile of CRP levels was associated with a relative risk of 2.10 (95% CI 1.04–41.18) and the highest quartile of IL-6 serum levels was associated with a relative risk of 1.81 (95% CI 0.97–3.36) for progression to advanced stages of AMD [147]. On the other hand, the pathophysiology of drusen and AMD is intricately linked to inflammation. A histologic study of drusen-covered eyes revealed the

presence of macrophages in addition to complement deposits [148]. The production of several factors, including hypoxia-inducible factors (HIFs), is known to cause monocyte migration. HIF1 promotes the synthesis of several proangiogenic molecules, such as vascular endothelial growth factor-A (VEGF-A), as well as immune system modifiers including monocyte chemoattractant protein-1 (MCP-1) and TNF-α, each of which can draw myeloid cells to hypoxic regions. Fibrosis and blood vessel ingrowth are features of late AMD [148]. A range of cytokines, including IL-2, IFN-γ, and TNF-α, are secreted by M1 macrophages to support local immunity and their phagocytic activity. The development of blood vessels is supported by the so-called M2 macrophages, which are alternately activated. They release cytokines such as TGF-β and IL-10. M1 macrophages often decrease with age, but in contrast, M2 macrophages increase in older persons [149,150].

4.8. Cancers

Patients undergoing cancer treatment who have been diagnosed with COVID-19 generally possess factors associated with risk of death, which are similar to comorbid factors such as hypertension and cardiovascular diseases, advanced age, and male gender, as previously demonstrated [151]. In addition, patients who have received recent anti-tumor treatment may be at increased risk of severe COVID-19 [151,152]. According to some recently published studies, cancer patients are more vulnerable to the complications of COVID-19, but the susceptibility of cancer patients to SARS-CoV-2 infection has not yet been demonstrated [152,153]. Patients with COVID-19 were shown to have elevated levels of many cytokines during the early stages of the pandemic, including IL-6, IL-1, TNF-α, and IFNs [21]. IL-6, a proinflammatory cytokine with immunological functions, tissue regeneration, and metabolism, is a key player in this process despite the fact that more than 50 cytokines and growth factors have been linked to aberrant signaling reactions [154]. In this context, the JAK/STAT signaling pathway is considered one of the main potential pathways since IL-6 was also found to be abnormally hyperactivated in many different forms of cancer. In individuals with severe COVID-19, either CD4 lymphopenia-induced lymphocytic dysregulation or excessive production of proinflammatory cytokines downstream of IL-6 are responsible for immune dysregulation [155]. Patients with severe COVID-19 frequently have elevated levels of proinflammatory cytokines such as IL-2, IL-6, IL-7, IL-10, IFNs, and TNF-α [77]. Given that patients with severe COVID-19 and patients with

disseminated malignancies both showed excessive plasma IL-6 levels, it is feasible that IL-6 or one of its downstream components may be an effective target for COVID-19 therapy.

Type I IFN possesses an essential additional signaling mechanism. Both immune responses against cancer and viral infections require type I IFN responses [156]. Impaired type I IFN signaling is linked to tumor development because IFN is essential for preventing tumor growth and inducing tumor cell senescence and death [157]. In response to SARS-CoV-2 infection, type I IFN signaling was shown to be suppressed [32]. Additionally, peripheral blood samples from patients with severe or critical COVID-19 showed low levels of type I IFN and ISGs as well as increase in IL-6 and inflammatory responses [37].

Immune checkpoint signaling is the third signaling pathway that is typical for cancers and COVID-19 [158]. It is an immunosuppressive pathway that involves the interaction of immune checkpoint molecules expressed in immune cells (especially T cells) with their corresponding ligands responding to pathogens or cancerogenic cells. First, the major histocompatibility complex (MHC) on antigen presenting cells (APCs) is recognized by T cell receptors (TCRs) on antigen-specific T cells. Then, CD28 on T cells must send signals to APCs carrying CD80/CD86. To reduce the hyperactivation and length of the immune responses, a number of immune checkpoint molecules (receptors) and their associated ligands interact [158]. PD1, programmed cell death 1 ligand 1 (PDL1, also known as B7-H1) and cytotoxic T lymphocyte antigen 4 (CTLA4)-CD80/CD86 are the receptor-ligand combinations that have been the subject of most research. The question of whether immune checkpoint inhibitor (ICI) treatment for cancer patients carries an increased risk during the COVID-19 pandemic is still up for debate. Cytokine storms during SARS-CoV-2 infection cause T-cell hyperactivation, which leads to fatigue and is linked to concomitant lymphopenia [159]. There are still some issues regarding the use of ICI to treat COVID-19. Through ICI, worn-out T cells may be reactivated and develop immunological competence. However, revitalized T cells may also boost cytokine production and raise the possibility of the cytokine storm, which might ultimately result in harmful lesions in various organs [160].

4.9. Autoimmune diseases

When the immune system does not recognize auto-components, it produces autoantibodies against the body's own cells, tissues, or organs, causing inflammation, which leads to

autoimmune disease [161]. Regarding patients affected by SARS-CoV-2, its specific pathogenic mechanism of action is still not completely understood. However, there are reports in the literature of a patient who developed Systemic Lupus Erythematosus after infection with SARS-CoV-2 [162]. SARS-CoV-2 infections induce inflammatory cytokines, according to several studies [163]. Particularly, it has been suggested that this immune response might either assist in fighting viruses or increase the production of inflammatory chemokines, resulting in an "inflammatory storm" that could worsen the already serious conditions of patients [164]. The same process has been proven to cause familial chilblains and other autoimmune diseases like lupus for development of autoimmune diseases when type I IFNs are incorrectly activated in response to self-antigens or nucleic acid accumulation [100]. Low type I IFN blood levels and decreased type I ISG expression in white blood cells were linked to severe COVID-19 [101]. Therefore, it is probable that individuals with existing autoantibodies are more likely to develop severe COVID-19.

Figure 3 summarizes these considerations by presenting pathway-pathway interactions in COVID-19-associated comorbidity and long-term consequences with the focus on different diseases.
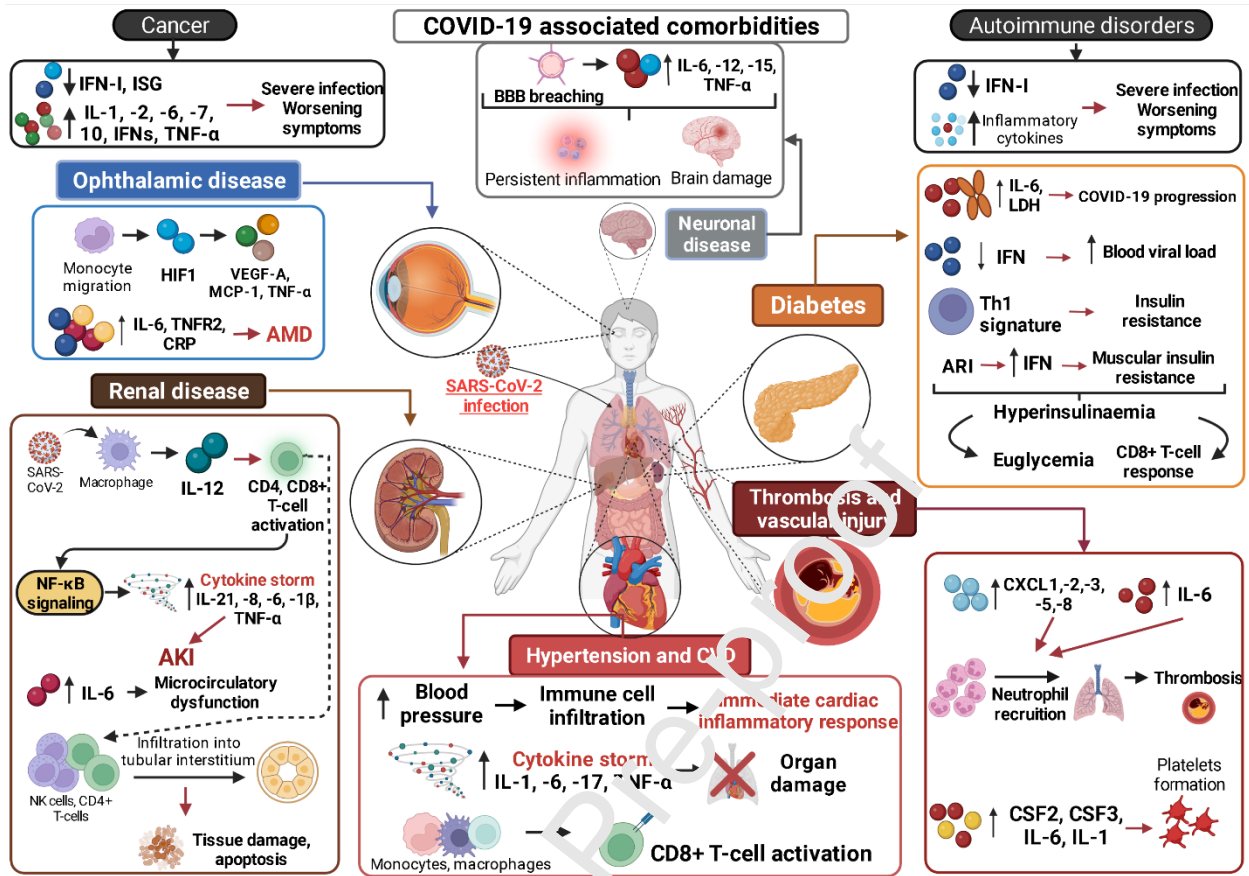
Figure 3: Pathway-pathway interactions in COVID-19-associated comorbidity and long-term consequences with the focus on different diseases. The figure has been created using BioRender (www.biorender.com)

5. SARS-CoV-2 signaling in cell proliferation and apoptosis

5.1 Modulating oncogenic pathways and implementation

Viruses have found strategies to target and modify essential biochemical pathways with a small number of proteins in order to proliferate. To counteract immune responses, viruses can alter the cell cycle, attract host DNA-damage machinery to replication sites, hijack host translation machinery, reduce apoptosis by dampening signaling pathways, and reprogram host epigenetic markers [165,166]. To regulate apoptosis and elude host protection, cancer cells and pathogens use comparable molecular processes. Infection with specific RNA or DNA viruses has been associated with oncogenesis by activation of cellular oncogenes or inhibition of tumor

suppressors. As a result, systemwide integration of protein–protein interactions that drive viral pathogenicity and cancer holds promise for identifying key factors that promote dysregulation of cellular mechanisms [25].

One of the hallmarks of cancer is dysregulation of cell-cycle control, since cancer cells continue to proliferate despite changes in pathways that provide continuous growth signals and permit evasion of cell-cycle arrest and apoptosis. Because viruses rely on their capacity to multiply in host cells to survive, it is no surprise that they disrupt the host cell cycle. Viruses can either terminate or accelerate cell division. A number of proteins associated with cell-cycle progression in the SARS-CoV-2 interactome has been identified, including proteins associated with the centrosome, mitotic spindle, and cytokinesis control [167]. Chemoinformatic analysis suggested that some anticancer drugs that have previously been licensed or are in clinical development can be effective against these proteins. Dabrafenib, a drug used to treat B-Raf Proto-Oncigene, Serine/Threonine Kinase (BRAF)-related malignancies, is thought to inhibit NIMA related protein kinase 9 (NEK9), a protein that interacts with SARS-CoV-2 NSP9. Furthermore, ponatinib and pazopanib are expected to suppress the activity of receptor-interacting serine/threonine protein kinase 1 (RIPK1), a SARS-CoV-2 NSP12 interactor linked to apoptosis, necroptosis, and inflammatory processes [167]. The avian coronavirus infectious bronchitis virus (IBV) has previously been demonstrated to cause cell-cycle arrest and replication stress by activating ATR-dependent DNA damage repair mechanisms [168]. Furthermore, ATR signaling inhibitors inhibited IBV replication. Replication stress activates the DNA damage signaling pathway, which is similar to the oncogene-induced phenomena seen in cancer cells. ATR-mediated signaling is increased in cancer cells with a faulty G1 checkpoint caused by mutation of TP53 or loss of RB1. Similarly, SARS-CoV causes cell-cycle arrest in the G1 phase via the retinoblastoma pathway, implying that ATR inhibitors might be used to treat COVID-19 [169].

Several SARS-CoV-2 viral proteins have been identified to interact with metabolic proteins [25]. Complex I interactions are particularly intriguing because metformin is known to inhibit this complex. Metformin treatment of SARS-CoV-2–infected cells led to a small reduction in viral load, suggesting that SARS-CoV-2 hijacks this complex for reproduction [167]. ETC is a generator of reactive oxygen species (ROS), and oxidative stress and ROS have a role in viral infection pathogenesis. Interactions with this pathway have been discovered, such as between

ORF3a and heme oxygenase 1 (HMOX1), as well as NSP14 and sirtuin 5 (SIRT5) [170]. NFE2-like bZIP transcription factor 2 (NFE2L2) interacts with the promoter of HMOX1 and promotes its expression. Under oxidative stress, the activity of NFE2L2 is controlled by Kelch-like ECH-associated protein 1 (KEAP1). Both NFE2L2 and KEAP1 are often mutated in lung cancer patients, emphasizing the pathway's relevance in tumor development [170]. SIRT5, an NSP14 interactor, has been found to control NFE2L2 transcriptionally, and increased SIRT5 levels in lung cancer contributing to tumor growth and treatment resistance [171]. SARS-CoV-2 might leverage these connections to disrupt essential mechanisms governing mitochondrial metabolism and oxidative stress, including pathways known to be important in tumor growth [25].

Viruses have developed mechanisms to modify the host epigenome in order to counteract host immune responses for efficient viral replication. Both viral infections and cancer growth have been linked to epigenetic alterations caused by histone methyltransferases and deacetylases [172]. The histone methyltransferase NSD2 interacts with NSP8, while the histone deacetylase HDAC2 interacts with NSP5. NSD2 and HDAC2 are linked via many carcinogenic mechanisms. NSD2 catalyzes the monomethylation and dimethylation of histone H3 Lys36 (H3K36), and enhanced NSD2 catalytic activity causes transcriptional alterations seen in cancers such as multiple myeloma, acute lymphoblastic leukemia, and solid tumors [173]. NSD2 also interacts with bromodomain-containing protein 4 (BRD4), a protein from the bromodomain and extra-terminal (BET) family. The SARS-CoV-2 E protein has been shown to interact with BRD4 and BRD2. BET proteins are highly conserved epigenetic readers and transcriptional regulators that are attracted to super enhancers in the chromatin, and hence play a role in antiviral signaling as well as modulating virus-induced inflammation [174]. BRD4 and BRD2 are human immunodeficiency virus (HIV) transcription suppressors in latently infected cells. As a result, BET protein inhibitors have been found to reverse HIV latency in cell lines and several primary cell models. A possible scenario for the interaction of SARS-CoV-2 E protein with host BET proteins suggests that the virus suppresses the activity of these proteins by sequestering them out of the nucleus. BET inhibitors may work as antiviral drugs by disrupting the interaction of the E protein with BET proteins. BET inhibitors exhibited either little or no impact on viral infection in SARS-CoV-2–infected cells *in vitro*, indicating that additional mechanistic research is needed [167]. Epigenetic alterations are widespread in cancer and can have a significant impact on the

transcriptional landscape of the cell. Understanding the mechanisms behind these alterations might speed up the repurposing of anticancer medications for COVID-19 therapy [25].

Viruses continue to develop new ways to capture and hijack the cellular translation machinery. The SARS-CoV NSP1 protein is known to bind to 40S ribosomes and preferentially promote endonucleolytic cleavage of host mRNAs [175]. One of these, La ribonucleoprotein 1 (LARP1), acts as a phosphorylation-sensitive switch that controls whether a collection of mRNAs with a 5′ terminal oligopyrimidine (TOP) motif are repressed or activated during translation [176]. LARP1 has been shown to promote carcinogenesis in malignancies, particularly those associated with viral infections and in the context of cancer, mammalian target of rapamycin (mTOR) signaling is one of the interactors and regulators of LARP1 [176]. A set of substrates, including LARP1, bind to eukaryotic initiation factor 4 E (eIF4E) and control TOP mRNA translation. Rapamycin is an FDA-approved drug that prevents LARP1 from binding to mTORC1 and is already being used to treat a variety of malignancies. Sapanisertib, a small molecule mTOR inhibitor, is now being studied in clinical trials for breast cancer, lung cancer, and other advanced solid tumors. In vitro, neither of them showed antiviral efficacy as monotherapeutic drugs [167]. However, zotatifin, an inhibitor of host mRNA translation, inhibited SARS-CoV-2 infection in *in vitro* models, indicating that viral replication is dependent on host mRNA translation [167]. Additionally, zotatifin and tomivosertib are now in clinical development for solid tumors.

Centrosome-associated proteins, nuclear pore proteins, ER quality control proteins, RNA processing proteins, respiratory electron transport proteins, and Ras-associated binding (RAB) signaling proteins have been identified as key targets of SARS-CoV-2 [25]. The enormous number of drugs which have been used for the treatment of diverse cancer types opens up the possibility of therapeutic repurposing. For example, cancer medications like midostaurin and ruxolitinib are also potential inhibitors of human proteins targeted by SARS-CoV-2. They target microtubule affinity regulating kinase (MARK) -2 and -3, which are important in controlling microtubule stability and cell polarity. The transporter protein ATP-binding cassette subfamily C member 1 (ABCC1) is targeted by daunorubicin and verapamil, both of which boosted SARS-CoV-2 infection in vitro. Multiple cancer therapies are being tested using pevonedistat, a **c-Cbl conjugates neural precursor cell-expressed, developmentally downregulated 8** (NEDD8)

inhibitor. Silmitasertib inhibits casein kinase 2 alpha 2 (CSNK2A2), a serine/threonine protein kinase involved in stress granule modulation [25].

5.2 SARS-CoV-2 modulated apoptosis and its implementation

Cell death pathways have been postulated to play an important role in SARS-CoV-2 infection [177]. Programmed cell death can be subverted by viruses. Furthermore, viruses can evade the host immune response. The programmed cell death and inflammation are mainly controlled by proteins of the death domain (DD) superfamily, which comprises the DD, death effector domain (DED), caspase activation recruitment domain (CARD), and pyrin domain (PYD) subfamilies [178]. Thus, the target of the DD proteins of the extrinsic pathway could play an essential role in viral infection regarding inflammation control and be capable of restoring the innate immune response. The extrinsic cell death pathway is triggered through death receptors (DRs) [179]. The key signaling platforms involved in induction of cell death through CD95 and DR4/5 and SARS/SARS-CoV-2 infection, as well as their cross-talk are illustrated in Figure 4.

A recent study has demonstrated that the ORF3a protein of SARS-CoV-2, a key accessory protein encoded by this virus, induces apoptosis in cells. Thus, these findings extend our knowledge of ORF3a, which will probably help to shed light on the pathogenicity of SARS-CoV-2 [180].
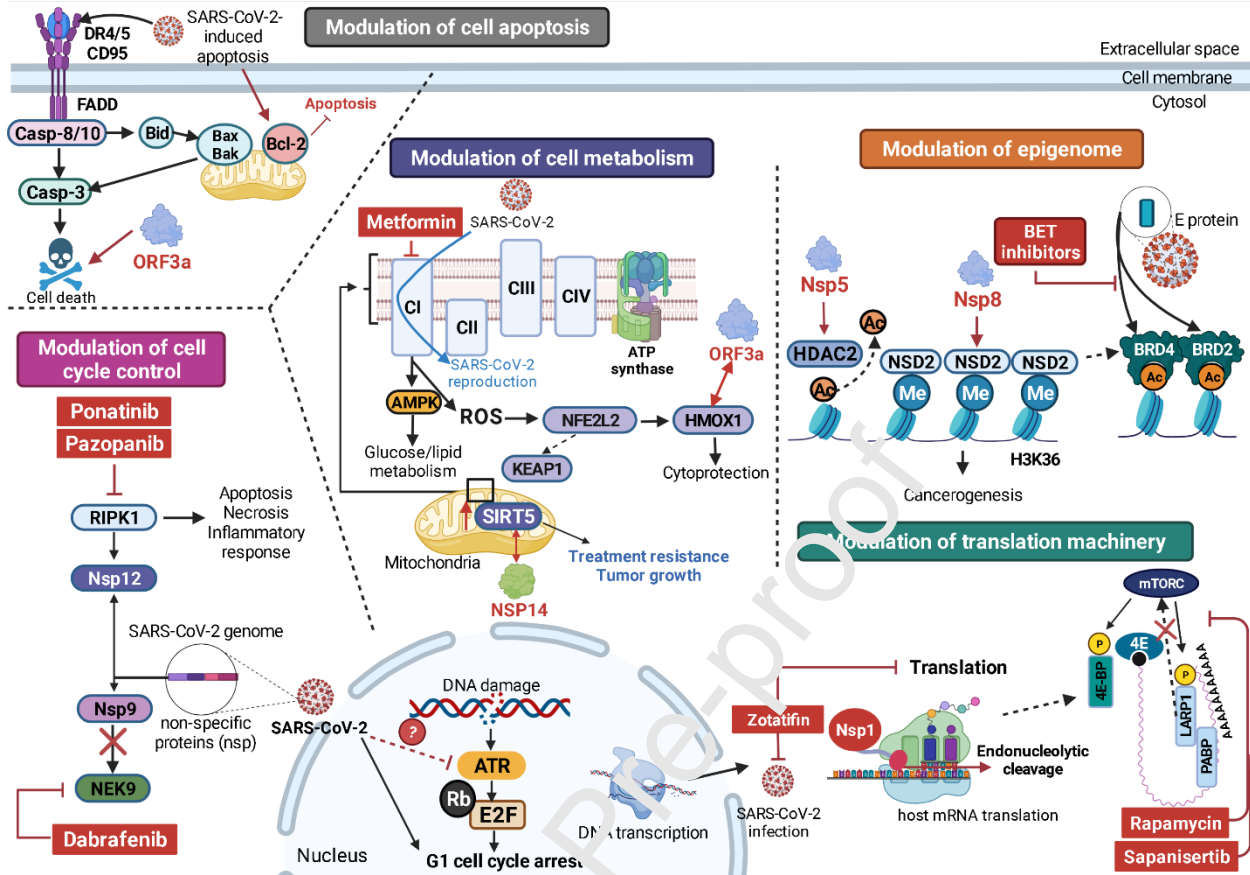
Figure 4: Overview of SARS-CoV-2 signaling in cell proliferation and apoptosis. The figure has been created using BioRender (www.biorender.com)

6. Conclusion

The COVID-19 signalome presents a significant impact on pathways associated with SARS-CoV-2 infection, the deregulation of pathways in tissues and organs of infected individuals, and pathways affecting comorbidity and long-term consequences of COVID-19. In this review, we have tried to dissect the relevant signaling pathways. In the case of SARS-CoV-2 infection, it has been well documented that its infection is mediated by ACE2, the functional receptor for SARS-CoV-2 and other coronaviruses. It has also been established that SARS-CoV-2 can hijack the cellular COP1 protein for retrograde trafficking of its S protein through the ER and Golgi compartments. Related to the Raf/MEK/ERK pathway, it was demonstrated that the SARS-CoV S protein stimulated COX2 expression, suggesting a possible role for Raf/MEK/ERK in SARS-

CoV-2 survival also providing a potential therapeutic strategy against COVID-19. In the context of immune escape pathways, it has been shown that SARS-CoV-2 can efficiently counteract host antiviral systems. For example, IFN response inhibition by SARS-CoV-2 not only prevents antiviral actions of ISGs, but also affects innate and adaptive immune responses. However, some controversy has been described for IFN in relation to SARS-CoV-2 infections [101]. In this context, SARS-CoV-2 can induce over but delayed type I IFN responses, whereas for example SARS-CoV-2 ORF6 seems to inhibit IFN production [32]. Moreover, imbalanced inflammatory responses against SARS-CoV-2 can lead to low levels of type I and III IFN production [33] and increased COVID-19 pathology [34]. Additionally, analysis of the kinetics of IFN plasma levels in COVID-19 patients demonstrated peak levels of IFN at day 8-10 of COVID-19 symptom onset [101]. Generally, IFN levels decreased with time. However some patients showed no IFN expression indicating a poorer outcome.

Moreover, SARS-CoV-2 infections have been characterized by the induction of inflammation leading to epithelial damage and organ injuries contributing to cytokine storms. SARS-CoV-2 infection has also been associated with changes in the lipid composition in cell membranes facilitating viral entry. Additionally, SARS-CoV-2 infections have been linked to heterologous T-cell immunity against common bacterial infections. Moreover, it has been established that SARS-CoV-2 share pathways with several pathogenic protozoans.

In the context of pathways in host tissues and organs, SARS-CoV-2 infections can cause their deregulation and induce innate and adaptive immune responses. Related to the heart, it has been reported that COVID-19 patients have suffered from late-onset cardiovascular complications such myocarditis-like alterations. Moreover, other organs affected are lung, kidney, liver, brain, eye, and skin.

Much attention has focused on comorbidity issues related to SARS-CoV-2 infections and the long-term consequences of COVID-19. In the context of diabetes, several studies have indicated a high prevalence of COVID-19 in diabetics probably due to compromised IFN responses, damaged caused to DNA by elevated IL-6 levels, and a potential association between ACE2 and control of hyperglycemia. COVID-19 has also been linked to abnormal clotting, thrombosis, and microvascular lesions due to abnormal expression of cytokines and chemokines. Furthermore, it has been shown that in COVID-19 patients with ARDS microvascular thrombosis might be

responsible for the high mortality rate. Heart failure and arrhythmia are comorbid cardiovascular diseases generating complications in COVID-19 patients. Also, as hypertension has been associated with a significantly higher risk of respiratory infection, it influences the severity of COVID-19. Renal injury and induced death of tubular epithelial cells have been linked to enhanced COVID-19 mortality. Moreover, accumulation of SARS-CoV-2 antigens in renal tubules has been discovered in post-mortem kidneys. COVID-19 has also caused long-term effects in the central and peripheral nervous systems. SARS-CoV-2 has also been shown to be responsible for the production of inflammatory molecules such as cytokines, chemokines and other inflammatory agents in stimulated glial cells. In the area of ophthalmology, it has been demonstrated that COVID-19 enhances the risk of developing AMD due to the elevated levels of pro-inflammatory cytokines such as IL-6 and TNF-α receptor 2. In the context of cancers, patients who have received anti-cancer drugs may have an increased risk of acquiring severe COVID-19 although enhanced susceptibility to SARS-CoV-2 infections has not been confirmed, so far. Finally, related to autoimmune diseases, although SARS-CoV-2 infections induce inflammatory cytokines, which might assist in fighting viral infections, the enhanced inflammatory chemokine production might provoke an "inflammatory storm", which could worsen the prognosis of the patient.

In the context of SARS-CoV-2 signaling and cell proliferation and apoptosis, viruses are capable of altering the host cell cycle, taking over the host cell translation machinery, and reducing apoptosis by through interaction with signaling pathways and reprogramming host epigenetic markers. Specific DNA and RNA viruses have been demonstrated to activate cellular oncogenes or inhibit tumor suppression. Investigation of protein-protein interaction on a systemwide scale might allow identification of key components for viral pathogens and cancers. Finally, as programmed cell death , mainly controlled by the DD superfamily proteins, plays a crucial role in SARS-CoV-2 infections, targeting cell death pathways could be essential for controlling viral infections and inflammation, and for restoring the innate immune responses.

In this review, we have demonstrated the importance of the COVID-19 signalome by describing various pathways involved in SARS-CoV-2 infection and infection and their impact on COVID-19 comorbidity. Although plenty of knowledge has been acquired since the appearance of the SARS-CoV-2 at the end of 2019, additional information is required for more effective COVID-

19 treatment with a possibility for its complete eradication. As it looks now, we have entered a phase where SARS-CoV-2 has become endemic and to cope with it and be prepared for any novel emerging outbreaks we need to be alert and up to date with the latest information.

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