Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

CHAPTER NINE

Interaction between Sars-CoV-2 structural proteins and host cellular receptors: From basic mechanisms to clinical perspectives

Henry Wade, Qihua Duan, and Qiaozhu Su*

Institute for Global Food Security, School of Biological Sciences, Queen's University Belfast, Belfast, United Kingdom

*Corresponding author: e-mail address: q.su@qub.ac.uk

Contents

Advances in Protein Chemistry and Structural Biology, Volume 132
ISSN 1876-1623
https://doi.org/10.1016/bs.apcsb.2022.05.010

Abstract

Severe acute respiratory syndrome coronavirus 2 (Sars-CoV-2) has caused a global pandemic that has affected the lives of billions of individuals. Sars-CoV-2 primarily infects human cells by binding of the viral spike protein to angiotensin-converting enzyme 2 (ACE2). In addition, novel means of viral entry are currently being investigated, including Neuropillin 1, toll-like receptors (TLRs), cluster of differentiation 147 (CD147), and integrin $\alpha 5\beta 1$. Enriched expression of these proteins across metabolic regulatory organs/tissues, including the circulatory system, liver, pancreas, and intestine contributes to major clinical complications among COVID-19 patients, particularly the development of hypertension, myocardial injury, arrhythmia, acute coronary syndrome and increased coagulation in the circulatory system during and post-infection. Pre-existing metabolic disease, such as cardiovascular disease, obesity, diabetes, and non-alcoholic fatty liver disease, is associated with increased risk of hospitalization, persistent post-infection complications and worse outcomes in patients with COVID-19. This review overviews the biological features of Sars-CoV-2, highlights recent findings that delineate the pathological mechanisms of COVID-19 and the consequent clinical diseases.

Abbreviation

aa	amino acid
ACE2	angiotensin converting enzyme 2
Ang	angiotensin
Cat	cathepsin
CCL	chemokine ligand
CD147	cluster of differentiation 147
COVID-19	Coronavirus disease 2019
E protein	envelope protein
GI	gastrointestinal
HT	hypertension
IBD	inflammatory bowel disease
IFN	interferon
IL	interleukin
LDL	low-density lipoprotein
M protein	membrane protein
Mas	mitochondrial assembly
mtDNA	mitochondrial DNA
mTOR	mammalian target of rapamycin
N protein	nucleocapsid protein
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NF-κb	nuclear factor kappa B

NRP	neuropillin
NSP	non-structural protein
ORF	open reading frame
PAH	pulmonary arterial hypertension
PP	polyprotein
RAAS	renin angiotensin aldosterone system
RdRP	RNA-dependent RNA polymerase
RGD	Arg-Gly-Asp
ROS	reactive oxygen species
RTC	replication and transcription complex
S protein	spike protein
Sars-CoV-2	severe acute respiratory syndrome Coronavirus 2
SgRNA	subgenomic RNA
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TLR	Toll-like receptor
TMPRSS2	transmembrane serine protease 2
TNF	tumor necrosis factor
TRAF	tumor necrosis factor receptor-associated factor
TRS	transcription regulatory sequence

1. Genome, proteins and life cycle of Sars-CoV-2

1.1 Genome of Sars-Cov-2

Severe acute respiratory syndrome-coronavirus-2 (Sars-CoV-2) is a positive-sense, single-stranded RNA, enveloped virus belonging to the family Coronaviridae, subfamily Orthocoronavirinae (Masters, 2006) Sars-CoV-2 possesses a remarkably large viral genome of ~30 kb in length. The genome is divided into fourteen open reading frames (ORFs) flanked by cis-acting secondary RNA structures necessary for RNA synthesis at the 5′- and 3′-untranslated regions. The fourteen ORFs of Sars-CoV-2 encode 29 viral proteins, including sixteen non-structural proteins (NSPs), which are encoded within two overlapping polyproteins (pp1a and pp1ab) that span the 5′ two-thirds of the viral genome (Chen, Liu, & Guo, 2020; Kim et al., 2020). The four canonical structural proteins (the spike, envelope, nucleocapsid, and membrane proteins) are encoded within the remaining third of the genome towards the 3′-untranslated region. Interspersed between the structural protein genes are genes encoding

accessory proteins which assist in viral infection and replication: ORF3a, ORF3b, ORF6, ORF7a, ORF7b, ORF8b, ORF9b and ORF10.

2. Key proteins of Sars-CoV-2

2.1 Spike (S) protein

The spike (S) protein, a trimeric type I membrane protein, protrudes from the Sars-CoV-2 virion surface and is necessary for recognition of the host cells and initiation of viral fusion into host cells. The heavily glycosylated S proteins of coronaviruses are among the largest recorded, with that of Sars-Cov-2 being 1237 amino acids in length (180–200 kDa) (Huang, Yang, Xu, Xu, & Liu, 2020; Ou et al., 2020). This S protein is divided into two subunits: S1 and S2.

S1 subunit: S1 of the S protein possesses an N-terminal domain and a receptor binding domain (RBD). The RBD of S1 is necessary for host-virus interaction and exists in one of two conformations. In the low energy state of this subunit, termed the "down" state, the RBD is concealed by being angled towards the internal cavity of the trimeric S protein, thus offering protection to this important domain. Upon interaction with the host, the S1 subunit changes conformation via a hinge-like mechanism to reveal the binding site of the RBD and promote S-protein-host-receptor interaction.

S2 subunit: S2 of the S protein composed of four distinct regions: a fusion peptide, two heptad repeats termed HR1 and HR2, and a transmembrane domain. The helical stalk of S2 is formed primarily of HR1 (Tang, Bidon, Jaimes, Whittaker, & Daniel, 2020; Xia, Zhu, Liu, et al., 2020). A unique evolved characteristic of the Sars-CoV-2 virus, compared to that of its most closely related and well-studied counterpart, Sars-CoV, is a polybasic cleavage site (PRRAR) at the S1-S2 boundary that permits efficient cleavage of the S protein by furin protease (Budhraja, Pandey, Kannan, Verma, & Venkatraman, 2021; Peacock et al., 2021; Whittaker, 2021). Proteasomal digestion of the S protein is essential to internalization of the virus and the evolution of this new polybasic cleavage site may be key to the high infectivity, pathogenicity and zoonotic transmission of Sars-CoV-2. Within S2 is a further cleavage site termed S2′, immediately downstream from which is a fusion peptide (Lai, Millet, Daniel, Freed, & Whittaker, 2017). Of note, S2′ cleavage, but not S1 or S2 cleavage is essential to initiate internalization of the virus.

2.2 Envelope (E) protein

The envelope (E) protein is the smallest structural protein of Sars-CoV-2, being only 8–12 kDa. The E protein is composed of three primary domains: a short hydrophilic N-terminus of 7–12 amino acids; a hydrophobic transmembrane domain ~25 amino acids in length; and a longer hydrophobic C-terminus (Schoeman & Fielding, 2019). The E protein assists viral lysis and subsequent release of the viral genome upon cellular internalization of a virion. In a host cell, the E protein localizes to the endoplasmic reticulum (ER) and Golgi membranes to assist in viral assembly and budding, and to form pentameric ion channels, with little or no selectivity, to enhance viral replication (Corse & Machamer Carolyn, 2000; Nieto-Torres et al., 2014). Notably, E protein mediated pumping of $Ca2+$ ions out of the ER enhances cellular inflammation and may be a significant factor in the unusually large immune response to Sars-CoV-2 infection.

2.3 Nucleocapsid (N) protein

The nucleocapsid (N) protein is the only structural protein within the virion, which protects and localizes the RNA genome towards the membrane by packaging it into a ribonucleoprotein complex (Cubuk et al., 2021). The N protein is composed of two structurally conserved domains: the N-terminal domain and the C-terminal domain; the prior being a monomer, the latter being a dimer (Ye, Lu, & Corbett, 2021). The N-terminal domain is characterized by a positively charged protrusion to facilitate putative RNA binding. This RNA binding characteristic of the N protein allows a degree of protection from intracellular host immune responses as the N protein can suppress RNAi-mediated antiviral responses (Cui et al., 2015).

2.4 Membrane (M) protein

The membrane (M) protein is the most abundant structural protein of Sars-CoV-2, which is the protein to which all other structural proteins bind. The M protein spans the virion lipid membrane and leaves a short NH2-terminal protruding from the virion and a long COOH terminus within the virion (Thomas, 2020). It is interaction between the M and N proteins that promote completion of viral assembly by stabilizing the N protein RNA complex inside the virion (Bianchi et al., 2020).

3. Lifecycle of Sars-CoV-2

3.1 Entry of Sars-CoV-2

Entry of Sars-CoV-2 into the host is initiated by the RBD within S protein of Sars-CoV-2 that interacts with host ACE2 receptor (Yang et al., 2020; Zamorano Cuervo & Grandvaux, 2020). Proteolytic cleavage of the S protein by host-cell-derived proteases is essential to permit fusion of the virus with the host cell membrane. Typically, this is facilitated by transmembrane serine protease 2 (TMPRSS2), with optional catalysis by endosomal cysteine protease cathepsin B (CatB) and/or cathepsin L (CatL) (Padmanabhan, Desikan, & Dixit, 2020; Qiao et al., 2021; Zhao et al., 2021, 2022). Furthermore, the aforementioned novel polybasic furin protease cleavage site between subunits S1 and S2 allows efficient cleavage of the S protein by furin in addition to TMPRSS2 and CatB/L. *In vitro*, it has been demonstrated that TMPRSS2 is preferred over CatB/L for S protein cleavage as inhibition of TMPRSS2 alone is sufficient to block entry of Sars-CoV-2 into primary lung cells (Hoffmann et al., 2020). Means of Sars-CoV-2 invading host cells via relevant protein machinery are utilized in Fig. 1.

***ACE2*:** The ACE2 receptor is expressed across more than 15 organ systems including the lungs, heart, kidneys, gastrointestinal (GI) tract, adipocytes, and pancreas. ACE2 is a component in the renin-angiotensin-aldosterone system (RAAS) (Reynolds et al., 2020): a homeostatic regulator of vascular function. In the RAAS pathway, renal juxtaglomerular cells release renin which cleaves angiotensin to angiotensin-I (AngI), which through the action of angiotensin converting enzyme (ACE) generates angiotensin-II (AngII); a powerful vasoconstrictor and the main effector of the RAAS pathway (Wu et al., 2018). ACE2 functions as a dipeptidyl carboxypeptidase within this system to convert AngII into Ang (1–7), AngI into Ang (1–9), and to hydrolyze peptides (Kuba, Imai, & Penninger, 2013). The primary recognized function of ACE2 is to lower blood pressure via its primary product Ang (1–7), an enzyme that promotes vasodilation by binding the mitochondrial assembly (Mas) receptor (Xu et al., 2017).

***TMPRSS2*:** TMPRSS2 is a 492 amino acid (aa) transmembrane protease of the Hepsin/TMPRSS subfamily of type II transmembrane serine proteases. TMPRSS2 contains an S1 family serine protease domain followed by a scavenger receptor cysteine rich domain. Additionally, there is a low-density lipoprotein receptor class A domain, a predicted transmembrane domain,

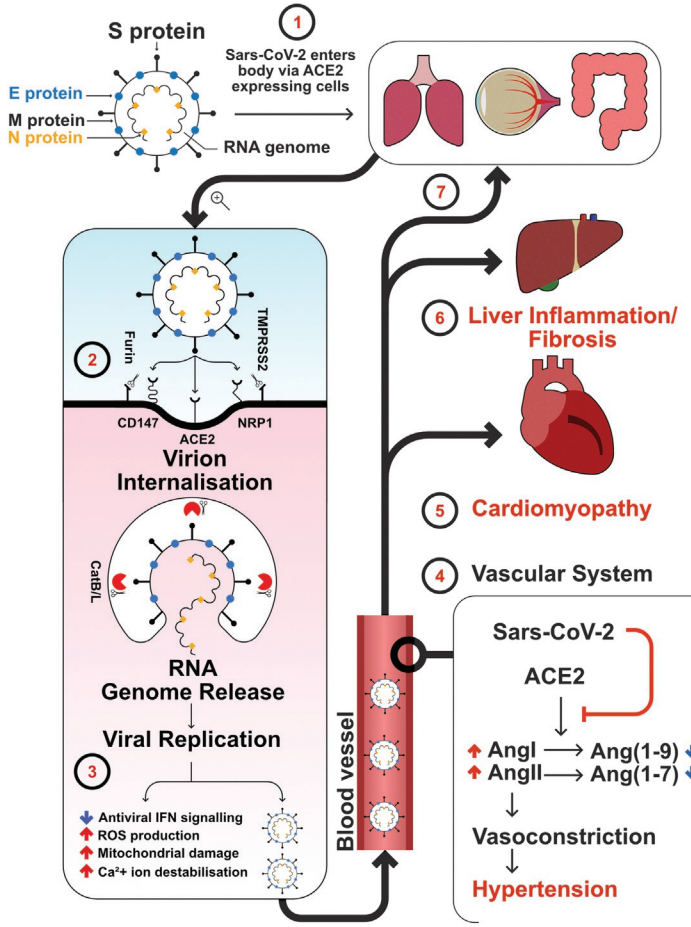

Fig. 1 Sars-CoV-2 induces cardiovascular dysfunction via ACE2 and enhances NAFLD (1) Sars-CoV-2 enters the body via the ACE2 expressing epithelia of the eyes, lungs, and digestive system. (2) Sars-CoV-2 enters cells by binding between the viral S-protein and host-cell surface proteins ACE2, CD147, or NRP1. Digestion of the S-protein by Furin and/or TMPRSS2 is essential for viral internalization. The viral RNA genome is released to facilitate replication and translation of viral proteins that assemble as new viral particles. (3) Translation of viral proteins induces downregulation of antiviral IFN signaling, upregulation of ROS production, mitochondrial damage, and destabilization of calcium ion homeostasis. (4) Newly synthesized virions are released into circulation where the S-protein of Sars-CoV-2 competes with vasoconstrictors AngI and AngII for ACE2 causing accumulation of AngI and AngII and the consequently chronic vasoconstriction, leading to hypertension. (5) Sars-CoV-2 infects the contractile cardiomyocytes of the heart, inducing cardiomyopathy. (6) Sars-CoV-2 infects hepatocytes of the liver, enhancing inflammation and promoting fibrogenesis, particularly in NAFLD/NASH patients. (7) Newly synthesized virions further target the eyes, lungs and the digestive system to amplify the pathological conditions.

and a cytoplasmic domain. TMPRSS2 is expressed across various organs including respiratory system, gastrointestinal system, liver, kidneys, pancreas, prostate, and thymus (Shen, Mao, Wu, Tanaka, & Zhang, 2017). TMPRSS2 primes the Sars-CoV-2 S protein by proteolytic cleavage (Abbasi et al., 2021). Substantial evidence has supported the notion of upregulation of TMPRSS2 expression by androgen may be a mechanism for the observed greater COVID-19 severity in men compared to women, suggesting that agents that downregulate or block androgen mediated TMPRSS2 activity may ameliorate COVID-19 severity (Bonafê et al., 2020; Deng, Rasool, Russell, Natesan, & Asangani, 2021; Qiao et al., 2021; Wambier & Goren, 2020).

***Cathepsin*:** Cathepsins are versatile protease enzymes that function within the low pH environment of lysosomes. CatB and CatL are both cysteine proteases: CatB is 339 aa and in its mature state is composed of a 25–26 kDa heavy chain and 5 kDa light chain. CatL is of similar size and structure being 333 aa in length. In addition to lysosomal activity, Cathepsins are also secreted from cells, allowing CatL to function as a matrix-degrading enzyme associated with chronic inflammation. Expression of CatL is upregulated in COVID-19 and overexpression of CatL in human cell lines increases viral pathogenicity (Zhao et al., 2021).

***Furin*:** Furin is known to cleave some glycoproteins from viral enveloped and increase viral fusion into cells. Furin belongs to the family of Ca^{2+}-dependent protein/prohormone convertases expressed ubiquitously across human tissue and recognizes the R-X-K/R-R peptide motif (Vankadari, 2020). Furin cleavage of the Sars-CoV-2 S protein has been demonstrated to be critical for Sars-CoV-2 replication and pathogenicity as data showed that loss of the furin cleavage site dramatically reduces viral pathogenicity (Johnson et al., 2020).

***Neuropillin-1*:** The Neuropillin 1 (NRP1), a type I cell surface receptor, is a novel means of entry for Sars-CoV-2 (Cantuti-Castelvetri, Ojha, Pedro, et al., 2020; Cantuti-Castelvetri, Ojha, Pedro Liliana, et al., 2020; Daly James et al., 2020). NRP1 is 130 kDa and composed of 850 aa. The structure is highly conserved among vertebrates: it is composed of five structural motifs (a1, a2, b1, b2, and c) that form an ectodomain mosaic. The protein N-terminus contains the tandem CUB domains (a1/a2) adjacent to tandem coagulation factor domains (b1/b2). The remainder of the ectodomain is comprised of the "c" member proximal MAM domain common among metalloproteinases and the N-termini of receptor protein tyrosine phosphatases (Yelland & Djordjevic, 2016). NRP1 is significant in development of

the circulatory and nervous systems, influencing angiogenesis by stabilizing vascular endothelial growth factor and its receptor (Lampropoulou & Ruhrberg, 2014; Lee et al., 2002). As such, NRP1 is highly expressed in arteries including the aorta. *In vitro*, it has been demonstrated that, in the absence of ACE2, NRP1 alone is not sufficient to allow entry of Sars-CoV-2, however, presence of NRP1 increases efficiency of Sars-CoV-2 intake (Cantuti-Castelvetri, Ojha, Pedro, et al., 2020; Daly James et al., 2020). Thus, NRP1 expressing tissues, such as those in the circulatory system, are of increased susceptibility to Sars-CoV-2 infection.

***CD147*:** Similarly, the transmembrane glycoprotein, cluster of differentiation (CD147), has been identified as a novel means of host cell entry for Sars-CoV-2 (Wang, Chen, Zhang, et al., 2020). Direct interaction between the Sars-CoV-2 S protein and host CD147 has been observed in vitro and overexpression of CD147 promotes viral infection. Furthermore, expression of CD147 in a cell line that is resistant to Sars-CoV-2 infection due to diminished ACE2 is sufficient to enable Sars-CoV-2 entry into cells (Wang, Chen, Zhou, et al., 2020). However, these claims have been disputed with negative results produced by a second research team (Shilts, Crozier, Greenwood, Lehner, & Wright, 2021). Further investigation is needed to determine the role of CD147 in Sars-CoV-2 infection. Though, of note, CD147 expression is enhanced on cardiomyocytes originating from the hypertrophied left ventricle of transverse-aortic constriction mice (Zhong et al., 2022). This enhancement of CD147 in constricted heart tissue may promote Sars-CoV-2 infection in the cardiovascular system during later stages of COVID-19, and may help explain the association between heart diseases—including hypertension (HT) and arrhythmia—and COVID-19.

***Integrin α5β1*:** Integrins are cell adhesion receptors that comprise 24 αβ heterodimers and are capable of recognizing glycoproteins and cell surface/extracellular matrix ligands. α5β1 is an Arg-Gly-Asp (RGD)-binding integrin expressed by endothelial and epithelial cells (Schaffner, Ray, & Dontenwill, 2013). α5β1 typically acts as a fibronectin receptor and is demonstrated as a facilitator of Sars-CoV-2 cell entry by α5β1-RGD-Sars-CoV-2-RBD binding (Robles et al., 2022).

3.2 Genome transcription and translation

Upon entry of the virus into the host cell, the positive-sense single stranded RNA genome is released to allow translation. Translation of ORF1a and

ORF1b yield two polyproteins, pp1a and pp1ab, from which the sixteen NPSs of the virus are cleaved. Pp1a encodes NSP1-11 whilst pp1ab, which is approximately 1.4 times larger, contains NSP1-10 and NSP12-16 (Chen et al., 2020; V'kovski, Kratzel, Steiner, Stalder, & Thiel, 2021). Release of NSPs from these polyproteins is achieved by proteolytic cleavage by cysteine proteases located within NSP3 and NSP5; release of NSP1 occurs particularly rapidly to enhance viral replication by blocking mRNA export from the host cell nucleus: NSP1 interacts with host mRNA export receptor, the heterodimer NXF1-NXT1 that is necessary for export of nuclear mRNAs. This frees up host ribosomes for translation of viral genes (Zhang et al., 2021).

NSP12-16 compose the viral replication and transcription complex (RTC), containing the core enzymatic functions required for RNA synthesis, RNA proofreading, and RNA modification. It is NSP12, an RNA-dependent RNA polymerase (RdRP) that is essential to further RNA synthesis whilst NSP7 and NSP8 function as cofactors (Naydenova et al., 2021; Peng et al., 2020); NSP14 provides a 3′-5′ exonuclease activity that assists RNA synthesis with a unique proofreading function (Smith, Blanc, Vignuzzi, & Denison, 2013).

The yet to be fully elucidated coronavirus capping machinery is composed of NSP10 (Viswanathan et al., 2020), which functions as a cofactor, NSP13, which provides the RNA 5′-triphosphatase activity (Ivanov et al., 2004), and NSP14 and NSP16, which perform the functions of N7-methyltransferase and 2′-O-methyltransferase respectively (Chen et al., 2009; Vithani et al., 2021). One key enzyme typically involved in the formation of the 5′ cap structure, the guanylyl transferase, has not yet been identified in coronaviruses

3.3 Structural and accessory proteins of Sars-CoV-2

Structural protein genes are encoded in the 3′-third of the RNA genome (Chen et al., 2020). Coronavirus structural proteins assemble and assist in the budding of new virions at the ER-to-Golgi compartments that are suggested to exit the infected cells by exocytosis. Some data suggests β-coronaviruses such as Sars-CoV-2 exit cells via the lysosomal trafficking pathway (Chen et al., 2021).

Between the ORFs of structural protein genes are interspersed accessory protein genes. At least five ORFs encoding accessory genes are encoded in Sars-CoV-2: ORF3, ORF6, ORF7a, ORF7b, ORF8, and ORF9

(Davidson et al., 2020; Finkel et al., 2021). Additionally, ORF10 is postulated to be downstream of the N protein gene (Pancer et al., 2020). However, not all of these are experimentally verified. Accessory genes display high variability among coronavirus groups and usually show no sequence homology with other viral and cellular proteins. Although they are not required for virus replication in cell culture, to some extent, they are conserved within their respective virus species and are suspected to have an important role in virus-host interactions. A common characteristic among Sars-CoV-2 accessory proteins is inhibition of the host cellular antiviral interferon (IFN) response; Sars-CoV-2 accessory proteins are detailed below:

***ORF3*:** ORF3 consists of three family members. ORF3a—The largest accessory protein of Sars-CoV-2 and an integral membrane viroporin that forms ion channels that may promote viral release. It is 275 aa in length and consists of an N-terminal domain, transmembrane domain, and a C-terminal domain folded as an 8-strand barrel (Yu et al., 2004; Yuan et al., 2005). Furthermore, ORF3a presents a TRAF3-binding motif that activates the NLRP3 inflammasome and is a potent stimulator of pro-interleukin (IL)-1β transcription (Siu et al., 2019). ORF3a has been identified as pro-apoptotic in host cells. ORF3b—Primarily localized to the cytoplasm, and is a potent IFN antagonist of 22 aa in length. Inhibition of IFN-1 by ORF3b is associated with disturbing the translocation of IFN1B transcription factor IRF3 to the nucleus (Konno et al., 2020). ORF3c—Function of ORF3c is unclear, however it possesses a conserved transmembrane domain that might suggest lipid bilayer membrane interaction (Jungreis, Sealfon, & Kellis, 2021).ORF3d—The nucleotide sequence of ORF3d overlaps other ORF3 genes from the 5′ of ORF3a to the 3′ or ORF3c. ORF3d is a 57 aa protein of unknown function that interacts with mitochondrial stomatin-like protein 2 (Redondo, Zaldívar-López, Garrido, & Montoya, 2021).

***ORF6*:** ORF6 is composed of 61 aa in length and localizes to membrane-bound organelles including the ER, lysosomes, and vesicles. It acts as an IFN antagonist by interfering with migration of transcription factor STAT to the nucleus, thus blocking IFN activation (Kopecky-Bromberg, Martínez-Sobrido, Frieman, Baric, & Palese, 2007).

***ORF7*:** ORF7 consists of two family members. ORF7a—A type I transmembrane protein formed of 121 aa in a seven-stranded β-sandwich fold. ORF7a is polyubiquitinated at Lys 119, a modification believed to enhance the ability of ORF7a to interfere with the IFN-1 response by inhibition

of STAT2 (Li et al., 2020; Su et al., 2006; Xia, Cao, Xie, et al., 2020). Furthermore, ORF7a is observed to bind CD14+ monocytes, reducing their antigen presenting ability, but greatly inducing expression of pro-inflammatory cytokines (Zhou et al., 2021). *ORF7b*—The intended function is yet to be elucidated, but ORF7b is composed of 43 aa and localizes to the Golgi. It is believed not essential for viral replication and has been shown to induce expression of INF-β, IL-6, and tumor necrosis factor (TNF)α in addition to activating type-I IFN signaling via IF3 phosphorylation (Yang, Zhao, Rao, et al., 2021).

***ORF8*:** ORF8 is a 121 aa protein consisting of an N-terminal signal sequence followed by a predicted Ig-like fold (Flower Thomas et al., 2021). Whilst ORF8 expression is not essential to viral replication, it appears to function as an organizer of protein folding in the ER: ORF8 interacts with Torsin-1a (a protein folding quality controller in the ER). Furthermore, ORF8 modulates the unfolded protein response by upregulating ER-resident chaperones binding immunoglobulin protein 78 (Bip) and glucose regulated protein 94 as well as inducing activating transcription factor-6 and inositol requiring enzyme 1, but it does not appear to stimulate the PERK pathway (Rashid, Dzakah, Wang, & Tang, 2021; Valcarcel, Bensussen, Álvarez-Buylla, & Díaz, 2021).

***ORF9*:** ORF9 consists of three family members. ORF9b—There is conflicting nomenclature regarding ORF9b: this ORF has been inconsistently referred to as ORF9a or ORF9b. However, ORF9b has been proposed as the preferred name (Jungreis et al., 2021). Like other Sars-CoV-2 accessory proteins, ORF9b inhibits the IFN response. ORF9b achieves this by localizing to the mitochondrial membrane and reducing cellular tumor necrosis factor receptor-associated factor (TRAF) 3 and TRAF6 levels (Shi et al., 2014). Additionally, ORF9b forms a complex with mitochondrial membrane protein Tom70, a mitochondrial import receptor, consequently impairing cellular anti-viral response (Jiang et al., 2020). *ORF9c*–ORF9c also impairs cell antiviral response by interfering with the IFN response. Moreover, ORF9c interacts with sigma receptors associated with lipid remodeling and ER-stress, as well as nuclear factor (NF)-κB related proteins Nod-like receptor, proteinase activated receptor 2, and Nedd4 family interacting protein 2. The downstream influence of ORF9c is upregulation of MAPK/ERK2 pathway proteins and inhibited immune response caused by impairing antigen presentation and complement signaling (Dominguez Andres et al., 2020).

***ORF10*:** The protein is 38 aa in length. The function of ORF10 is unclear, however, believed to be unessential for viral replication and transmission (Pancer et al., 2020).

3.4 Replication compartments

In the early stages of Coronavirus infection, like many other positive-sense RNA viruses, the infected host cell experiences membrane reorganization with the formation of ER-derived and interconnected perinuclear double-membrane structures (V'kovski et al., 2021). These include double membraned vesicles, open double-membraned spherules, and convoluted membranes. It is the direct interaction between coronavirus NSPs and host cell factors that induced biogenesis of these specialized organelles termed replication compartments or replication organelles. Mechanism for the formation of replication compartments is not fully understood. In Sars-CoV-2 infection, it is proposed that the membrane spanning NPSs, NSP3, NSP4, and NSP6 are responsible for manipulating host membranes into the observed replication compartments (Oudshoorn et al., n.d.; Angelini, Akhlaghpour, Neuman, & Buchmeier, 2013).

Replication compartment formation is a conserved characteristic among coronaviruses that serves to provide a favorable niche rich in necessary macromolecules for RNA synthesis whilst shielding viral replication intermediates from cytosolic immune sensors. It is known that Sars-CoV-2 replicase subunits (NSP3, NSP5, NSP8) anchor themselves to convoluted membranes, however, the exact location of viral RNA replication remains unknown (Ulasli, Verheije, de Haan, & Reggiori, 2010). Upon formation, double-stranded RNA migrates to the interior of double-membrane vesicles via NSP3 formed pores to potentially render newly synthesized viral RNAs available for translation and encapsidation into virions (Wolff et al., 2020). It is unclear when double-stranded viral RNA is separated to form the final single-stranded RNA genome.

3.5 RNA transcription

NSP12-16 comprise the core functions of viral RNA synthesis, proofreading, and modification. The RNA-dependent RNA polymerase (RdRP) residing in NSP12 is the centrepiece of coronavirus RTC and has been suggested as a promising drug target as it is a crucial enzyme in the virus lifecycle both for replication of the viral genome and also for transcription

of subgenomic RNAs (sgRNAs) (Naydenova et al., 2021; Peng et al., 2020). Structure of Sars-CoV-2 NSP12 and its cofactors NSP7 and NSP8 show high conservation and similarity with that of Sars-CoV with more than 95% similarity (Biswal et al., 2021). NSP12 is composed of three domains: a Nidovirus RdRP-associated nucleotidyl-transferase domain, a right-handed RdRP domains, and an interface domain (Dwivedy et al., 2021). Viral genomic replication is initiated by synthesis of full-length negative-sense genomic copies which function as templates for the generation of new positive-sense genomic RNA. Newly synthesized genomes are used for translation of more NSPs and RTCs or are packaged into new virions.

Characteristic of coronaviruses, and other members of the Order Nidovirales, is the discontinuous transcription process: in which, a set of nested 3′ to 5′ co-terminal sgRNAs are produced (Kim et al., 2020; Sola, Almazán, Zúñiga, & Enjuanes, 2015). During negative-strand RNA synthesis, the RTC interrupts transcription upon encountering transcription regulatory sequences (TRSs) located upstream to most ORFs in the third of the genome adjacent to the 3′ end. At TRS elements (TRS body), synthesis of negative-strand RNA stops and is re-initiated at the TRS adjacent to a leader sequence (TRS-L) located ∼70 nucleotides from the 5′ end of the genome. The discontinuous step of coronavirus RNA synthesis involves interaction between complementary TRSs of the nascent negative strand RNA (negative sense TRS body) and the positive strand genomic RNA (positive sense-TRS-L). Upon re-initiation of RNA synthesis at the TRS-L region, a negative strand copy of the leader sequence is added to the nascent RNA to complete the synthesis of the negative-strand sgRNAs. Creation of negative-strand RNA in this discontinuous manner occurs via production of a set of negative-strand subgenomic RNAs that act as templates for synthesis of positive-sense subgenomic mRNAs; these are translated into structural and accessory proteins. Although the coronavirus subgenomic mRNAs are structurally polycistronic, it is assumed that they are functionally monocistronic and only the first ORF at the 5′ end, absent in the next smaller sgRNA, is translated from each sgRNA (Sola et al., 2015).

4. Molecular mechanisms underlying Sars-CoV-2 induced pathological conditions

Sars-CoV-2 infection increases expression of coagulation markers which favors development of stroke, myocardial infarction, and ischemic

diseases, potentially inducing multiple organ dysfunction or failure (Ruiz-Ares et al., 2021). More profound complications extend to thrombosis in large parts of circulation including deep veins, arteries, and cardiac chambers (Long, Brady, Koyfman, & Gottlieb, 2020). This is enhanced by the exceptionally aggressive innate immune response experienced during COVID-19, termed the "cytokine storm", which perpetuates a hypercoagulable state. Individuals with coronary artery disease are at higher risk of complications (e.g., venous thromboembolism and arterial thromboembolism) due to the cytokine storm and exhibit inflamed plaque instability and rupture post Sars-CoV-2 infection (Pan et al., 2021; Song, Li, Xie, Hou, & You, 2020). Additionally, myocarditis is observed in COVID-19 patients, during and after infection, and is associated with impaired cardiac performance that potentially persists indefinitely (Shchendrygina, Nagel, Puntmann, & Valbuena-Lopez, 2021).

4.1 Cytokine storm induced by Sars-CoV-2

Points-of-contact for the Sars-CoV-2 virus are the ACE2 expressing mucus membranes/epithelia of the respiratory system, gastrointestinal system, and eyes. However, the virus has been observed penetrating organs across the body, being identified in biopsies of heart, liver, intestinal, and pancreatic tissues among many others, including immune privileged tissues (e.g., the brain and testes) (Trypsteen, Van Cleemput, Snippenberg, Gerlo, & Vandekerckhove, 2020). Sars-CoV-2 is believed to enter circulation via lesions of the alveoli. Additionally, the virus circulates through the circulatory system partly protected from the immune surveillance of the immune cells within the blood, a trait also observed in Sars-CoV which displays high infectivity of blood cells, macrophages, fibroblasts, and pericytes (Butler et al., 2022; Misiti, 2021). Furthermore, Sars-CoV-2 virion particles have been found in the circulatory system within extracellular vesicles containing the ACE2 receptor.

Upon Sars-CoV-2 tissue infection, there is a prompt infiltration of the pericardium, myocardium, and endocardium by immune cells, including neutrophils, pro-inflammatory monocytes, macrophages, and lymphocytes, converge on sites of viral infection. Cardiomyocytes infected with Sars-CoV-2 have increased expression of chemokine ligand 2 (CCL2), CCL3, and CXC-chemokine ligand 10, thus enhancing monocyte recruitment and secretion of cytokines (Law, Lee, Cheung, Yim, & Lau, 2007; Yang, Nilsson-Payant, Han, et al., 2021). This induces release of

pro-inflammatory cytokines, including monocyte chemoattractant protein-1, IL-1β, IL-6, and TNFα. IL-1β is a key regulator of the inflammatory response and simulates the release of other cytokines, such as IL-17, IL-21, and IL-22. IL-1β and TNFα, contribute to COVID-19 associated pain that often manifests as a severe headache and joint pain by inducing cyclooxygenase-2 in the nervous system. Such pain is observed to persist for several weeks after COVID-19 infection (Song et al., 2020).

In the myocardium, the elevated cytokines contribute to myocardial dysfunction and cardiac disease, for example, IL-1β may promote cell proliferation and contribute to cardiomyopathy by thickening layers of heart tissue (Bujak & Frangogiannis, 2009). Activation of the thrombin and complement system in COVID-19 has been found to induce endothelial lesions via excessive accumulation of platelets and white blood cells at sites of Sars-CoV2 infection. This contributes to coagulopathy with elevated D-dimer and fibrin degradation products, leading to micro thrombi (Magro et al., 2020).

The other largely released cytokines, such as TNFα, IFNγ, and IL-4, promote cellular pro-inflammatory pathways via different cytokine receptors. For example, binding of TNFα to the TNFα receptor 1 (TNFR1) recruits several adaptor proteins, out of which TRADD-containing complex activates the IKK complex, thus resulting in IκBα phosphorylation and subsequent ubiquitin-dependent proteasomal degradation and activation of NF-κB (Shi & Sun, 2018). Subsequently, this further activates several well-studied inflammatory and apoptotic signaling pathways, including c-Jun-N-terminal kinase and p38 mitogen activated protein kinases, caspase 8, and the NF-κB pathways that all together damage the cardiomyocytes. In addition, the release of IL-4 is often associated with cardiac fibrosis during HT and heart failure (Peng et al., 2015). Activation of these pathways can further signal through the mammalian target of rapamycin (mTOR) to initiate autophagy in cardiomyocytes.

Virus-induced cell-mediated autoimmune responses can lead to myocarditis and edema of the myocardial interstitial connective tissue. Myocarditis can progress to dilated cardiomyopathy (DCM). DCM patients who harbor cardiotropic viruses and coupled with myocarditis have a much poorer prognosis. Epidemiological studies show myocarditis is present in 20-30% of COVID-19 patients (Akhmerov & Marbán, 2020). Recent studies show COVID-19 patients with cardiovascular disease possessed anti-cardiolipin antibody (Jizzini, Shah, & Zhou, 2020), which against cardiolipin, an inner component of the mitochondrial membrane, and considered an indicator of cellular damage and myocardial injury (Dudek, 2017).

4.2 Perturbation of calcium ion homeostasis by Sars-CoV-2

Calcium is a major secondary messenger in cellular physiology, regulating countless metabolic processes and pathways. Many viruses are capable of co-opting and manipulating host calcium ion systems to support their own replication and survival (Chen, Cao, & Zhong, 2019; Zhou, Frey, & Yang, 2009). The essential role of Ca^{2+} ions in ATP synthesis and neuronal signaling for muscle contraction suggest dysfunction of Ca^{2+} ion homeostasis induced by Sars-CoV-2 infection would contribute to the reduced contractility of cardiomyocytes and general dysfunction of cardiac muscle observed in COVID-19.

In Sars-COV-2 infected endothelial cells, there is reduced expression of voltage-dependent anion channel (VDAC): an ion channel permeable to small solutes such as Ca^{2+} and a regulator of mitochondrial Ca^{2+} flux. Reduction in endothelial cell Ca^{2+} concentrations override release of vasodilator mediators and exacerbates endothelial dysfunction. Furthermore, upregulation of TLR-9 induced by Sars-CoV-2 infection inhibits ER/sarcoplasm reticulum Ca^{2+}-ATPase (SERCA2) activity, leading to reduced uptake of Ca^{2+} into the ER and mitochondria of cardiomyocytes and neurons (Costa et al., 2022; Wang et al., 2015).

4.3 Sars-CoV-2 infection induced mitochondrial oxidative stress

Mitochondria play a central role in host immune responses to viral infection. Mitochondrial dysfunction leads to release of mitochondrial DNA (mtDNA) which is a serious damage associated molecular pattern (DAMP) and the consequently significant induction of inflammation and cytokines. Sars-Cov-2 infection induces mitochondrial dysfunction, including increased production of reactive oxygen species (ROS) and mtDNA, reduced plasma Ca^{2+} concentrations and elevated circulating mtDNA concentrations (Costa et al., 2022).

Changes in mitochondrial membrane potential during mitochondrial dysfunction disrupts synthesis of ATP, induces membrane depolarization, and promotes mitochondrial swelling. *In vitro* infection of endothelial HUVEC cells by Sars-CoV-2 showed elevated gene expression of several components of the electron transport chain and mitochondrial ATP synthesis, including cytochrome B and NADH dehydrogenase. Furthermore, injury-associated intracellular enzyme LDH was also increased upon Sars-CoV-2 infection, suggesting the association between Sars-CoV-2 and mitochondrial damage (Costa et al., 2022).

4.4 Activation of TLR signaling by Sars-CoV-2

COVID-19 patients display elevated plasma mtDNA concentrations which induces immune response via activation of TLR9 (Zhang, Liu, Liu, Ren, & Sun, 2014). TLR9 also responds to unmethylated CpG repeats in RNA, which allow TLR9 to be activated by Sars-CoV-2 RNA that has unmethylated CpG motifs within the E-ORF and ORF10 nucleotide sequences, and mtRNA (Kumar et al., 2022). Similarly, TLR3, TLR7, and TLR8 show high binding affinity to Sars-CoV-2 mRNA (Sartorius, Trovato, Manco, D'Apice, & De Berardinis, 2021). *In silico* studies highlight TLR9 to have no binding affinity to the Sars-CoV-2 S protein in contrast to the high binding affinity identified in TLR4, TLR6, and TLR1 (Choudhury, Das, Patra, & Mukherjee, 2021).

The extent to which TLR9 activation contributes to the hyper-inflammation observed in COVID-19 is unclear. However, when considering association between COVID-19 and cardiovascular disease, the exceptional enrichment of myocardial cells with mitochondria may be a major contributing factor to Sars-CoV-2 induced myocardial dysfunction. Further investigation is warranted to delineate the association between Sars-CoV-2 and inflammatory responses in COVID-19 patients.

5. Sars-CoV-2 induced pathological conditions via mediation of ACE2

5.1 Sars-CoV-2 targets the cardiovascular system

COVID-19 and hypertension: The vascular endothelium is a crucial interface between blood and tissue, and plays a critical role in modulating angiogenesis, blood coagulation, and vascular toning. Under viral assault, endothelial cells mediate important innate immune processes, promoting swelling by increasing blood flow, regulating leakage of plasma proteins, and permitting movement of neutrophils, monocytes, and lymphocytes to sites of tissue damage (Rajendran et al., 2013). Sars-CoV-2 induced endothelial dysfunction observed in COVID-19 patients is associated with disrupted coagulation, thrombosis, systemic endotheliitis, increased ROS production, NO deficiency, and elevated D-dimer concentrations (Al-Samkari et al., 2020; Green, 2020; Li et al., 2021).

HT is a major comorbidity among COVID-19 patients, this is also true specifically for pulmonary arterial hypertension (PAH): a progressive condition characterized by abnormally high blood pressure in the pulmonary

arteries with a median survival rate of 2.8 years from time of diagnosis if untreated. Development of HT/PAH in COVID-19 patients is believed to be a result of interference/co-opting of the ACE2 receptor. By competing with the ACE2 receptor against AngI and AngII, Sars-CoV-2 blocks conversion of these vasoconstricting angiotensins to their vasodilating metabolites Ang (1–7) and Ang (1–9), consequently promoting elevated blood pressure (Fig. 1.) (Carey, Wang, & Siragy, 2000; Gressens et al., 2021; Kuba et al., 2013). Clinically, this manifests with HT preceding hospitalization being the leading comorbidity in non-surviving COVID-19 patients (Devaux, Rolain, & Raoult, 2020; Tudoran et al., 2021).

Sars-CoV-2 competes with AngI and AngII for ACE2 (Verdecchia, Cavallini, Spanevello, & Angeli, 2020), thus Sars-CoV-2 directly contributes to deterioration of cardiovascular homeostasis by causing an accumulation of vasoconstricting ACE2 ligand, AngII: in the absence of ACE2, AngII will bind angiotensin II type 1 receptor (ET1R) and/or angiotensin II type 2 receptor (AT2R) (Carey et al., 2000; Eguchi, Kawai, Scalia, & Rizzo, 2018). The downstream impact of Sars-CoV-2-induced ACE2 reduction further increases the risk of cardiovascular disease and damage in the form of cardiomyocyte damage/death due to elevated ROS concentrations, apoptosis, hypertrophy and fibrosis, in addition to the classic alveolar damage associated with Sars-CoV viruses (Muñoz et al., 2014; Ye et al., 2007; Zhong et al., 2010). It was postulated that use of RAAS pathway modulators (e.g., ACEi and ARBs) which inhibit production/activity of Angiotensin II, may potentiate the upregulation of ACE2 receptor and increase risk of COVID-19 (Gressens et al., 2021).

COVID-19 and myocarditis: Cardiomyocytes, the primary contractile cells of the heart, are particularly vulnerable to assault by Sars-CoV-2. Cardiomyocytes express all the necessary machinery to enable invasion by Sars-CoV-2 including: ACE2, TMPRSS2, CatB, CatL, and novel means of cell entry including NRP1, CD147, and integrins ($\alpha 5\beta 1$) (Thum, 2020; Vidak, Javoršek, Vizovišek, & Turk, 2019; Wu, Sun, Trzeciakowski, Meininger, & Muthuchamy, 2006). Infection of the myocardium by Sars-CoV-2 has major implications on host mortality with infected cardiomyocytes displaying diminished contractility due to dysregulation of contractile protein expression and dysregulated Ca^{2+} homeostasis (Danta, 2021).

COVID-19 and Arrythmia: Arrhythmic electrocardiographic abnormalities in the atria and ventricles are also observed in patients infected with Sars-CoV-2, indicating unlocalized myocardial damage (Mountantonakis et al., 2021). This is likely due to myocarditis or direct virus-induced damage

to cardiomyocytes. Inflammation of the sinoatrial, atrioventricular nodes or Purkinje may also contribute to arrhythmia. In COVID-19 patients, such arrhythmia is typically recorded as ST-elevation myocardial infarction (STEMI) or NSTEMI, inverted T wave and inverted P wave (Long et al., 2020).

5.2 COVID-19 in obesity and type-2 diabetes

Susceptibility of individuals with metabolic disease to COVID-19 is complicated. For example, obese individuals and those with type-2 diabetes (T2D) often display a weakened immune system and generally increased risk of infection. These groups are at an increased risk of contracting COVID-19 and other infectious illnesses. COVID-19 severity, and consequently rates of hospitalization, are higher in people with type 1 diabetes mellitus (T1D), T2D, or obesity (Barron et al., 2020; Gao et al., 2020; Kwok et al., 2020). A large population-based study including 8885 COVID-19 patients analyzed the association between COVID-19 with various comorbid conditions, such as HT, obesity, diabetes, hyperlipidemia, and non-alcoholic steatohepatitis (NASH) has found strong association between these conditions and incidence of COVID-19, with NASH having the strongest association (Ghoneim, Butt, Hamid, Shah, & Asaad, 2020).

T2D and obesity are metabolic conditions characterized by insulin resistance and chronic low-grade metabolic inflammation (Ferlita et al., 2019; Su et al., 2009; Tam, Morais, & Santosa, 2020). Moreover, the extent of metabolic inflammation is further modified by adipokines, hepatokines, myokines, lipokines, branched-chain amino acids, and microbial metabolites, which may circulate at abnormal levels in some people with T2D or obesity (Stefan & Häring, 2013). Collectively, these acquired abnormalities broadly impair cellular immune function, likely contributing to enhanced activation of the NLR family pyrin domain containing 3 (NLRP3) inflammasome, and a greater susceptibility to infection in vulnerable individuals (Sharma & Kanneganti, 2021). There is considerable interest in whether the expression of viral entry factors essential for SARS-CoV-2 infectivity is enhanced in one or more tissues in patients with T2D or obese people; however, the available data are inconclusive.

The relationship between Sars-CoV-2 and T2D has been described as bidirectional: Sars-CoV-2 may induce de novo T2D in previously non-diabetic patients whilst pre-existing T2D acts as an independent predictor of COVID-19 mortality (Lim, Bae, Kwon, & Nauck, 2021). This is due to the insulin producing pancreatic β-cells expressing ACE2 which is the target of Sars-CoV-2.

There are conflicting reports on the expression of ACE2 in the liver of individuals with T2D: some observing decreased/unchanged hepatic ACE2 expression (Biquard, Valla, & Rautou, 2020), and others observing increased hepatic ACE2 expression (Meijnikman, Bruin, Groen, Nieuwdorp, & Herrema, 2021). Additionally, the effect of T2D on Sars-CoV-2 target proteins ACE2 and TMPRSS2 is observed to vary by sex: men with T2D display unchanged ACE2 and TMPRSS2 expression, whilst in women both proteins decreased compared to non-diabetic individuals. This could partly be explained by the role of androgens in upregulating TMPRSS2 and this is in line with the increased risk of clinical COVID-19 complications observed in men (Deng et al., 2021; Gagliardi, Tieri, Ortona, & Ruggieri, 2020).

Adiponectin (APN) is an adipocytokine that sensitizes insulin receptor signaling, stimulating mitochondrial biogenesis and suppressing inflammation. Pleiotropic effects of APN on multiple tissues are mediated through the membrane-bound adiponectin receptors AdipoR1 and AdipoR2. AdipoR1 sensitizes insulin receptor by inducing calcium influx to activate Ca^{2+}/calmodulin-dependent kinase, AMP kinase (AMPK), and NF-κB with mixed effects on inflammation depending on the circulating APN isoform (Gabler & Spurlock, 2007). Meanwhile, AdipoR2 binding stimulates PPARα signaling to influence fatty acid oxidation.

Obesity is associated with hypoadiponectinemia, which is related to APN gene variants and environmental factors. This phenotype is observed in both insulin-resistant and non-diabetic individuals as well as various insulin-resistant animal models (Prakash, Mittal, Awasthi, Agarwal, & Srivastava, 2013). Conceivably, as insulin resistance progresses to chronic T2D and APN resistance, the subsequence of compensatory hyperadiponectinemia might emerge, which could involve dysfunctional AdipoR2 signaling, a phenotype observed in an insulin-resistant transgenic mouse model (Bauche et al., 2006). Accordingly, it has been proposed that Sars-CoV-2 induced pattern recognition triggers complex inflammatory signaling, transforming hypoadiponectinemia to pathological hyperadiponectinemia (Ho et al., 2021).

5.3 COVID-19 in non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is a broad term encompassing a variety of liver pathological conditions, including hepatic steatosis, NASH, liver fibrosis and liver cirrhosis (Kumar, Duan, Wu, Harris, & Su, 2021). Generally, NAFLD is associated with abnormal accumulation of lipids in

the liver that results from increased de novo lipogenesis, high adipose tissue lipolysis, and insulin resistance. As such, NAFLD is intrinsically associated with T2D and obesity.

Frequent mild liver injury is observed in patients with COVID-19, while patients with NAFLD had a higher chance of developing severe COVID-19 (Sarin et al., 2020). A retrospective study conducted on 202 COVID-19 patients admitted to hospital has reported liver injury in 50% of patients during admission, which increased to 75.2% during hospitalization (Huang, Zhu, Xue, et al., 2020). The injury mainly occurred on hepatocytes. Huang et al. further report that, in 280 COVID-19 patients, 30.7% of the patients had NAFLD whilst 35.7% had abnormal liver function at the time of hospital admission. However, the patients with or without NAFLD developed comparable complications and other clinical outcomes and no liver failure occurred during hospitalization. A retrospective case-control study has also reported similar observation which identified NAFLD among 31% of COVID-19 patients (Huang, Zhu, Wang, et al., 2020).

In a subgroup of NAFLD patients, fibrosis was reported as an additional major risk factor (Targher et al., 2020). ACE2 exhibits anti-inflammatory and anti-fibrotic effects, so under transition from relatively mild non-fibrotic NAFLD such as hepatic steatosis to the more severe fibrotic NAFLD such as NASH, ACE2 expression may change. This is consistent with observations in which ACE2 and TMPRSS2 expression has been shown to correlate with NAFLD disease score (Fondevila et al., 2021).

Sars-CoV-2 entry factors, including ACE2 and TMPRSS2, are differently affected by T2D compared to NAFLD. In obese women, those with T2D have significantly lower expression of ACE2 and TMPRSS2 compared to obese women without T2D. In contrast, obese individuals with NASH have higher expression of both ACE2 and TMPRSS2 compared to obese individuals without NASH. This demonstrates that different forms of metabolic syndrome will have different effects on the susceptibility of people to COVID-19, and that the advanced stages of NAFLD may specifically predispose patients to COVID-19 (Fondevila et al., 2021).

5.4 COVID-19 in inflammatory bowel disease

In the gastrointestinal system, ACE2 is expressed in the oral mucosa, the esophagus, stomach, pancreas, duodenum, ileum, colon, and rectum (Lehmann et al., 2021). In the intestine specifically, ACE2 is expressed at

the epithelial brush border, muscularis mucosa, muscularis propria, microvascular endothelium, and vascular smooth muscle. In human intestinal biopsies, catalytic activity of ACE2 is identified as higher in the terminal ileum compared to the colon; ACE2 controls bicarbonate secretion and absorption of dietary ions and glucose (Ferreira-Duarte, Estevinho, Duarte-Araújo, Magro, & Morato, 2020). Also, in the colon, AngII regulates motility to promote contraction of the colon. ACE2 product Ang (1–7) has anti-inflammatory and antifibrotic effects in the gastrointestinal system (Zizzo et al., 2017).

These factors make the GI system a prime site for infection by Sars-CoV-2. Individuals with inflammatory bowel disease (IBD) are at increased risk of COVID-19 complications with evidence of IBD patients suffering COVID-19 being significantly higher risk of developing venous thromboembolism. There is a 2–3-fold increased risk of developing venous thromboembolism in IBD patients compared to the healthy population in a hospitalized setting (Mahmud et al., 2021).

6. Conclusions

COVID-19 is most commonly associated with the characteristic development of severe acute respiratory symptoms. However, the extensive expression of ACE2 throughout tissues of the circulatory system and metabolic regulatory organs has led to growing recognition of secondary COVID-19 complications and comorbidities including cardiovascular disease, T2D, NAFLD, and potentially IBD. Particular attention should be paid to the long-term and permanent impact of COVID-19 on the cardiovascular system, in which, Sars-CoV-2 can induce exceptional damage by disrupting the RAAS system that regulates blood pressure. Additionally, novel interactions between the Sars-CoV-2 S protein and cellular receptors and proteins have highlighted several potential means of cellular entry for Sars-CoV-2, including NRP1, TLRs, and integrins.

7. Future perspective

Development of COVID-19 therapies was initially limited due to poor understanding of the virus (Cao et al., 2020; López-Medina et al., 2021; Mitjà et al., 2021). However, several effective agents have since been made available including Molnupiravir (Jayk Bernal et al., 2022), Paxlovid (Mahase, 2021), and Remedisvir (Gottlieb et al., 2022), which have been

endorsed by the FDA and EUA. Additionally, the corticosteroid dexamethasone is indicated as an effective agent for reducing the hyperinflammation induced by the cytokine storm (Horby et al., 2021); similarly, immune treatment including anti-IL-6 monoclonal antibodies, IL-1 antagonists, and Janus kinase inhibitors are being utilized to ease COVID-19 associated inflammation (Conti et al., 2020; Huet et al., 2020; Michot et al., 2020; Richardson et al., 2020). Currently vaccines are being utilized as an effective preventative measure against the development of severe acute respiratory symptoms requiring hospitalization. However, there is controversy surrounding the ability of some vaccines to predispose individuals, e.g., those with IBD, to development of venous thromboembolism (Mahmud et al., 2021). Since obesity is one of the major risk factors uniting COVID-19 with metabolic disease and cardiovascular disease (Gao et al., 2020), it seems poignant to investigate the effectiveness of diet and lifestyle as a preventative measure against COVID-19.

Acknowledgments

Q. Su is supported by the British Heart Foundation (UK) (PG/19/86/34788) and Northern Ireland Chest Heart & Stroke (UK) (2019_08). H. Wade is a recipient of PhD research scholarships from the Department for the Economy in Northern Ireland (UK).

References

Abbasi, A. Z., Kiyani, D. A., Hamid, S. M., Saalim, M., Fahim, A., & Jalal, N. (2021). Spiking dependence of SARS-CoV-2 pathogenicity on TMPRSS2. *Journal of Medical Virology*, *93*(7), 4205–4218. https://doi.org/10.1002/jmv.26911.

Akhmerov, A., & Marbán, E. (2020). COVID-19 and the Heart. *Circulation Research*, *126*(10), 1443–1455. https://doi.org/10.1161/CIRCRESAHA.120.317055.

Al-Samkari, H., Karp Leaf, R. S., Dzik, W. H., Carlson, J. C. T., Fogerty, A. E., Waheed, A., et al. (2020). COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. *Blood*, *136*(4), 489–500. https://doi.org/10.1182/blood.2020006520.

Angelini, M. M., Akhlaghpour, M., Neuman, B. W., & Buchmeier, M. J. (2013). Severe acute respiratory syndrome coronavirus nonstructural proteins 3, 4, and 6 induce double-membrane vesicles. *MBio*, *4*(4). https://doi.org/10.1128/mBio.00524-13.

Barron, E., Bakhai, C., Kar, P., Weaver, A., Bradley, D., Ismail, H., et al. (2020). Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: A whole-population study. *The Lancet Diabetes & Endocrinology*, *8*(10), 813–822. https://doi.org/10.1016/S2213-8587(20)30272-2.

Bauche, I. B., Ait El Mkadem, S., Rezsohazy, R., Funahashi, T., Maeda, N., Miranda, L. M., et al. (2006). Adiponectin downregulates its own production and the expression of its AdipoR2 receptor in transgenic mice. *Biochemical and Biophysical Research Communications*, *345*(4), 1414–1424. https://doi.org/10.1016/j.bbrc.2006.05.033.

Bianchi, M., Benvenuto, D., Giovanetti, M., Angeletti, S., Ciccozzi, M., & Pascarella, S. (2020). Sars-CoV-2 envelope and membrane proteins: Structural differences linked to virus characteristics? *BioMed Research International*, *2020*, 4389089. https://doi.org/10.1155/2020/4389089.

Biquard, L., Valla, D., & Rautou, P.-E. (2020). No evidence for an increased liver uptake of SARS-CoV-2 in metabolic-associated fatty liver disease. *Journal of Hepatology*, *73*(3), 717–718. https://doi.org/10.1016/j.jhep.2020.04.035.

Biswal, M., Diggs, S., Xu, D., Khudaverdyan, N., Lu, J., Fang, J., et al. (2021). Two conserved oligomer interfaces of NSP7 and NSP8 underpin the dynamic assembly of SARS-CoV-2 RdRP. *Nucleic Acids Research*, *49*(10), 5956–5966. https://doi.org/10.1093/nar/gkab370.

Bonafè, M., Prattichizzo, F., Giuliani, A., Storci, G., Sabbatinelli, J., & Olivieri, F. (2020). Inflamm-aging: Why older men are the most susceptible to SARS-CoV-2 complicated outcomes. *Cytokine & Growth Factor Reviews*, *53*, 33–37. https://doi.org/10.1016/j.cytogfr.2020.04.005.

Budhraja, A., Pandey, S., Kannan, S., Verma, C. S., & Venkatraman, P. (2021). The polybasic insert, the RBD of the SARS-CoV-2 spike protein, and the feline coronavirus—Evolved or yet to evolve. *Biochemistry and Biophysics Reports*, *25*, 100907. https://doi.org/10.1016/j.bbrep.2021.100907.

Bujak, M., & Frangogiannis, N. G. (2009). The role of IL-1 in the pathogenesis of heart disease. *Archivum Immunologiae et Therapiae Experimentalis*, *57*(3), 165–176. https://doi.org/10.1007/s00005-009-0024-y.

Butler, D., Coyne, D., Pomeroy, L., Williams, P., Holder, P., Carterson, A., et al. (2022). Confirmed circulation of SARS-CoV-2 in Irish blood donors prior to first national notification of infection. *Journal of Clinical Virology*, *146*, 105045. https://doi.org/10.1016/j.jcv.2021.105045.

Cantuti-Castelvetri, L., Ojha, R., Pedro, L. D., Djannatian, M., Franz, J., Kuivanen, S., et al. (2020). Neuropilin-1 facilitates SARS-CoV-2 cell entry and provides a possible pathway into the central nervous system. *bioRxiv*. https://doi.org/10.1101/2020.06.07.137802. 2020.2006.2007.137802.

Cantuti-Castelvetri, L., Ojha, R., Pedro Liliana, D., Djannatian, M., Franz, J., Kuivanen, S., et al. (2020). Neuropilin-1 facilitates SARS-CoV-2 cell entry and infectivity. *Science*, *370*(6518), 856–860. https://doi.org/10.1126/science.abd2985.

Cao, B., Wang, Y., Wen, D., Liu, W., Wang, J., Fan, G., et al. (2020). A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. *The New England Journal of Medicine*, *382*(19), 1787–1799. https://doi.org/10.1056/NEJMoa2001282.

Carey, R. M., Wang, Z.-Q., & Siragy, H. M. (2000). Role of the angiotensin type 2 receptor in the regulation of blood pressure and renal function. *Hypertension*, *35*(1), 155–163. https://doi.org/10.1161/01.HYP.35.1.155.

Chen, Y., Cai, H., Pan, J. A., Xiang, N., Tien, P., Ahola, T., et al. (2009). Functional screen reveals SARS coronavirus nonstructural protein nsp14 as a novel cap N7 methyltransferase. *Proceedings of the National Academy of Sciences*, *106*(9), 3484–3489. https://doi.org/10.1073/pnas.0808790106.

Chen, X., Cao, R., & Zhong, W. (2019). Host calcium channels and pumps in viral infections. *Cell*, *9*(1), 94. https://doi.org/10.3390/cells9010094.

Chen, Y., Liu, Q., & Guo, D. (2020). Emerging coronaviruses: Genome structure, replication, and pathogenesis. *Journal of Medical Virology*, *92*(4), 418–423. https://doi.org/10.1002/jmv.25681.

Chen, D., Zheng, Q., Sun, L., Ji, M., Li, Y., Deng, H., et al. (2021). ORF3a of SARS-CoV-2 promotes lysosomal exocytosis-mediated viral egress. *Developmental Cell*, *56*(23), 3250–3263. e3255. https://doi.org/10.1016/j.devcel.2021.10.006.

Choudhury, A., Das, N. C., Patra, R., & Mukherjee, S. (2021). In silico analyses on the comparative sensing of SARS-CoV-2 mRNA by the intracellular TLRs of humans. *Journal of Medical Virology*, *93*(4), 2476–2486. https://doi.org/10.1002/jmv.26776.

Conti, P., Ronconi, G., Caraffa, A., Gallenga, C. E., Ross, R., Frydas, I., et al. (2020). Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): Anti-inflammatory strategies. *Journal of Biological Regulators and Homeostatic Agents*, *34*(2), 327–331. https://doi.org/10.23812/conti-e.

Corse, E., & Machamer Carolyn, E. (2000). Infectious bronchitis virus e protein is targeted to the golgi complex and directs release of virus-like particles. *Journal of Virology*, *74*(9), 4319–4326. https://doi.org/10.1128/JVI.74.9.4319-4326.2000.

Costa, T. J., Potje, S. R., Fraga-Silva, T. F. C., da Silva-Neto, J. A., Barros, P. R., Rodrigues, D., et al. (2022). Mitochondrial DNA and TLR9 activation contribute to SARS-CoV-2-induced endothelial cell damage. *Vascular Pharmacology*, *142*, 106946. https://doi.org/10.1016/j.vph.2021.106946.

Cubuk, J., Alston, J. J., Incicco, J. J., Singh, S., Stuchell-Brereton, M. D., Ward, M. D., et al. (2021). The SARS-CoV-2 nucleocapsid protein is dynamic, disordered, and phase separates with RNA. *Nature Communications*, *12*(1), 1936. https://doi.org/10.1038/s41467-021-21953-3.

Cui, L., Wang, H., Ji, Y., Yang, J., Xu, S., Huang, X., et al. (2015). The nucleocapsid protein of coronaviruses acts as a viral suppressor of RNA silencing in mammalian cells. *Journal of Virology*, *89*(17), 9029–9043. https://doi.org/10.1128/jvi.01331-15.

Daly James, L., Simonetti, B., Klein, K., Chen, K.-E., Williamson Maia, K., Antón-Plágaro, C., et al. (2020). Neuropilin-1 is a host factor for SARS-CoV-2 infection. *Science*, *370*(6518), 861–865. https://doi.org/10.1126/science.abd3072.

Danta, C. C. (2021). SARS-CoV-2, hypoxia, and calcium signaling: The consequences and therapeutic options. *ACS Pharmacology & Translational Science*, *4*(1), 400–402. https://doi.org/10.1021/acsptsci.0c00219.

Davidson, A. D., Williamson, M. K., Lewis, S., Shoemark, D., Carroll, M. W., Heesom, K. J., et al. (2020). Characterisation of the transcriptome and proteome of SARS-CoV-2 reveals a cell passage induced in-frame deletion of the furin-like cleavage site from the spike glycoprotein. *Genome Medicine*, *12*(1), 68. https://doi.org/10.1186/s13073-020-00763-0.

Deng, Q., Rasool, R. U., Russell, R. M., Natesan, R., & Asangani, I. A. (2021). Targeting androgen regulation of TMPRSS2 and ACE2 as a therapeutic strategy to combat COVID-19. *iScience*, *24*(3), 102254. https://doi.org/10.1016/j.isci.2021.102254.

Devaux, C. A., Rolain, J.-M., & Raoult, D. (2020). ACE2 receptor polymorphism: Susceptibility to SARS-CoV-2, hypertension, multi-organ failure, and COVID-19 disease outcome. *Journal of Microbiology, Immunology and Infection*, *53*(3), 425–435. https://doi.org/10.1016/j.jmii.2020.04.015.

Dominguez Andres, A., Feng, Y., Campos, A. R., Yin, J., Yang, C.-C., James, B., et al. (2020). SARS-CoV-2 ORF9c is a membrane-associated protein that suppresses antiviral responses in cells. *bioRxiv*. https://doi.org/10.1101/2020.08.18.256776. 2020.2008.2018.256776.

Dudek, J. (2017). Role of cardiolipin in mitochondrial signaling pathways [review]. *Frontiers in Cell and Development Biology*, *5*. https://doi.org/10.3389/fcell.2017.00090.

Dwivedy, A., Mariadasse, R., Ahmad, M., Chakraborty, S., Kar, D., Tiwari, S., et al. (2021). Characterization of the NiRAN domain from RNA-dependent RNA polymerase provides insights into a potential therapeutic target against SARS-CoV-2. *PLoS Computational Biology*, *17*(9), e1009384. https://doi.org/10.1371/journal.pcbi.1009384.

Eguchi, S., Kawai, T., Scalia, R., & Rizzo, V. (2018). Understanding angiotensin II type 1 receptor signaling in vascular pathophysiology. *Hypertension*, *71*(5), 804–810. https://doi.org/10.1161/HYPERTENSIONAHA.118.10266.

Ferlita, S., Yegiazaryan, A., Noori, N., Lal, G., Nguyen, T., To, K., et al. (2019). Type 2 diabetes mellitus and altered immune system leading to susceptibility to pathogens, especially mycobacterium tuberculosis. *Journal of Clinical Medicine*, *8*(12). https://doi.org/10.3390/jcm8122219.

Ferreira-Duarte, M., Estevinho, M. M., Duarte-Araújo, M., Magro, F., & Morato, M. (2020). Unraveling the role of ACE2, the binding receptor for SARS-CoV-2 in inflammatory bowel disease. *Inflammatory Bowel Diseases*, *26*(12), 1787–1795. https://doi.org/10.1093/ibd/izaa249.

Finkel, Y., Mizrahi, O., Nachshon, A., Weingarten-Gabbay, S., Morgenstern, D., Yahalom-Ronen, Y., et al. (2021). The coding capacity of SARS-CoV-2. *Nature*, *589*(7840), 125–130. https://doi.org/10.1038/s41586-020-2739-1.

Flower Thomas, G., Buffalo Cosmo, Z., Hooy Richard, M., Allaire, M., Ren, X., & Hurley James, H. (2021). Structure of SARS-CoV-2 ORF8, a rapidly evolving immune evasion protein. *Proceedings of the National Academy of Sciences*, *118*(2), e2021785118. https://doi.org/10.1073/pnas.2021785118.

Fondevila, M. F., Mercado-Gómez, M., Rodríguez, A., Gonzalez-Rellan, M. J., Iruzubieta, P., Valentí, V., et al. (2021). Obese patients with NASH have increased hepatic expression of SARS-CoV-2 critical entry points. *Journal of Hepatology*, *74*(2), 469–471. https://doi.org/10.1016/j.jhep.2020.09.027.

Gabler, N. K., & Spurlock, M. E. (2007). Adiponectin attenuates reactive oxygen species accumulation and NFkB translocation in human cardiac myocytes during inflammation. *The FASEB Journal*, *21*(5), A583. https://doi.org/10.1096/fasebj.21.5.A583-c.

Gagliardi, M. C., Tieri, P., Ortona, E., & Ruggieri, A. (2020). ACE2 expression and sex disparity in COVID-19. *Cell Death Discovery*, *6*(1), 37. https://doi.org/10.1038/s41420-020-0276-1.

Gao, F., Zheng, K. I., Wang, X.-B., Sun, Q.-F., Pan, K.-H., Wang, T.-Y., et al. (2020). Obesity is a risk factor for greater COVID-19 severity. *Diabetes Care*, *43*(7), e72–e74. https://doi.org/10.2337/dc20-0682.

Ghoneim, S., Butt, M. U., Hamid, O., Shah, A., & Asaad, I. (2020). The incidence of COVID-19 in patients with metabolic syndrome and non-alcoholic steatohepatitis: A population-based study. *Metabolism Open*, *8*, 100057. https://doi.org/10.1016/j.metop.2020.100057.

Gottlieb, R. L., Vaca, C. E., Paredes, R., Mera, J., Webb, B. J., Perez, G., et al. (2022). Early remdesivir to prevent progression to severe Covid-19 in outpatients. *The New England Journal of Medicine*, *386*(4), 305–315. https://doi.org/10.1056/NEJMoa2116846.

Green, S. J. (2020). Covid-19 accelerates endothelial dysfunction and nitric oxide deficiency. *Microbes and Infection*, *22*(4-5), 149–150. https://doi.org/10.1016/j.micinf.2020.05.006.

Gressens, S. B., Leftheriotis, G., Dussaule, J.-C., Flamant, M., Levy, B. I., & Vidal-Petiot, E. (2021). Controversial roles of the renin angiotensin system and its modulators during the COVID-19 pandemic [review]. *Frontiers in Physiology*, *12*. https://doi.org/10.3389/fphys.2021.624052.

Ho, G., Ali, A., Takamatsu, Y., Wada, R., Masliah, E., & Hashimoto, M. (2021). Diabetes, inflammation, and the adiponectin paradox: Therapeutic targets in SARS-CoV-2. *Drug Discovery Today*, *26*(8), 2036–2044. https://doi.org/10.1016/j.drudis.2021.03.013.

Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., et al. (2020). SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*, *181*(2), 271–280. e278. https://doi.org/10.1016/j.cell.2020.02.052.

Horby, P., Lim, W. S., Emberson, J. R., Mafham, M., Bell, J. L., Linsell, L., et al. (2021). Dexamethasone in hospitalized patients with Covid-19. *The New England Journal of Medicine*, *384*(8), 693–704. https://doi.org/10.1056/NEJMoa2021436.

Huang, Y., Yang, C., Xu, X.-F., Xu, W., & Liu, S.-W. (2020). Structural and functional properties of SARS-CoV-2 spike protein: Potential antivirus drug development for COVID-19. *Acta Pharmacologica Sinica*, *41*(9), 1141–1149. https://doi.org/10.1038/s41401-020-0485-4.

Huang, R., Zhu, L., Wang, J., Xue, L., Liu, L., Yan, X., et al. (2020). Clinical features of patients with COVID-19 with nonalcoholic fatty liver disease. *Hepatology Communications*, *4*(12), 1758–1768. https://doi.org/10.1002/hep4.1592.

Huang, R., Zhu, L., Xue, L., Liu, L., Yan, X., Wang, J., et al. (2020). Clinical findings of patients with coronavirus disease 2019 in Jiangsu province, China: A retrospective, multi-center study. *PLoS Neglected Tropical Diseases*, *14*(5), e0008280. https://doi.org/10.1371/journal.pntd.0008280.

Huet, T., Beaussier, H., Voisin, O., Jouveshomme, S., Dauriat, G., Lazareth, I., et al. (2020). Anakinra for severe forms of COVID-19: A cohort study. *Lancet Rheumatology*, *2*(7), e393–e400. https://doi.org/10.1016/s2665-9913(20)30164-8.

Ivanov, K. A., Thiel, V., Dobbe, J. C., van der Meer, Y., Snijder, E. J., & Ziebuhr, J. (2004). Multiple enzymatic activities associated with severe acute respiratory syndrome coronavirus helicase. *Journal of Virology*, *78*(11), 5619–5632. https://doi.org/10.1128/jvi.78.11.5619-5632.2004.

Jayk Bernal, A., Gomes da Silva, M. M., Musungaie, D. B., Kovalchuk, E., Gonzalez, A., Delos Reyes, V., et al., & Group, M. O.-O. S. (2022). Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients. *The New England Journal of Medicine*, *386*(6), 509–520. https://doi.org/10.1056/NEJMoa2116044.

Jiang, H.-W., Zhang, H.-N., Meng, Q.-F., Xie, J., Li, Y., Chen, H., et al. (2020). SARS-CoV-2 Orf9b suppresses type I interferon responses by targeting TOM70. *Cellular & Molecular Immunology*, *17*(9), 998–1000. https://doi.org/10.1038/s41423-020-0514-8.

Jizzini, M., Shah, M., & Zhou, K. (2020). SARS-CoV-2 and anti-cardiolipin antibodies. *Clinical Medicine Insights: Case Reports*, *13*. https://doi.org/10.1177/1179547620980381. 1179547620980381.

Johnson, B. A., Xie, X., Kalveram, B., Lokugamage, K. G., Muruato, A., Zou, J., et al. (2020). Furin cleavage site is key to SARS-CoV-2 pathogenesis. *bioRxiv: The Preprint Server for Biology*. https://doi.org/10.1101/2020.08.26.268854. 2020.2008.2026.268854.

Jungreis, I., Nelson, C. W., Ardern, Z., Finkel, Y., Krogan, N. J., Sato, K., et al. (2021). Conflicting and ambiguous names of overlapping ORFs in the SARS-CoV-2 genome: A homology-based resolution. *Virology*, *558*, 145–151. https://doi.org/10.1016/j.virol.2021.02.013.

Jungreis, I., Sealfon, R., & Kellis, M. (2021). SARS-CoV-2 gene content and COVID-19 mutation impact by comparing 44 Sarbecovirus genomes. *Nature Communications*, *12*(1), 2642. https://doi.org/10.1038/s41467-021-22905-7.

Kim, D., Lee, J.-Y., Yang, J.-S., Kim, J. W., Kim, V. N., & Chang, H. (2020). The architecture of SARS-CoV-2 transcriptome. *Cell*, *181*(4), 914–921. e910. https://doi.org/10.1016/j.cell.2020.04.011.

Konno, Y., Kimura, I., Uriu, K., Fukushi, M., Irie, T., Koyanagi, Y., et al. (2020). SARS-CoV-2 ORF3b is a potent interferon antagonist whose activity is increased by a naturally occurring elongation variant. *Cell Reports*, *32*(12), 108185. https://doi.org/10.1016/j.celrep.2020.108185.

Kopecky-Bromberg, S. A., Martínez-Sobrido, L., Frieman, M., Baric, R. A., & Palese, P. (2007). Severe acute respiratory syndrome coronavirus open reading frame (ORF) 3b, ORF 6, and nucleocapsid proteins function as interferon antagonists. *Journal of Virology*, *81*(2), 548–557. https://doi.org/10.1128/jvi.01782-06.

Kuba, K., Imai, Y., & Penninger, J. M. (2013). Multiple functions of angiotensin-converting enzyme 2 and its relevance in cardiovascular diseases. *Circulation Journal*, 77(2), 301–308. https://doi.org/10.1253/circj.cj-12-1544.

Kumar, S., Duan, Q., Wu, R., Harris, E. N., & Su, Q. (2021). Pathophysiological communication between hepatocytes and non-parenchymal cells in liver injury from NAFLD to liver fibrosis. *Advanced Drug Delivery Reviews*, *176*, 113869. https://doi.org/10.1016/j.addr.2021.113869.

Kumar, A., Goyal, N., Saranathan, N., Dhamija, S., Saraswat, S., Menon, M. B., et al. (2022). The slowing rate of CpG depletion in SARS-CoV-2 genomes is consistent with adaptations to the human host. *Molecular Biology and Evolution*, *39*(3), msac029. https://doi.org/10.1093/molbev/msac029.

Kwok, S., Adam, S., Ho, J. H., Iqbal, Z., Turkington, P., Razvi, S., et al. (2020). Obesity: A critical risk factor in the COVID-19 pandemic. *Clinical Obesity*, *10*(6), e12403. https://doi.org/10.1111/cob.12403.

Lai, A. L., Millet, J. K., Daniel, S., Freed, J. H., & Whittaker, G. R. (2017). The SARS-CoV fusion peptide forms an extended bipartite fusion platform that perturbs membrane order in a calcium-dependent manner. *Journal of Molecular Biology*, *429*(24), 3875–3892. https://doi.org/10.1016/j.jmb.2017.10.017.

Lampropoulou, A., & Ruhrberg, C. (2014). Neuropilin regulation of angiogenesis. *Biochemical Society Transactions*, *42*(6), 1623–1628. https://doi.org/10.1042/bst20140244.

Law, A. H. Y., Lee, D. C. W., Cheung, B. K. W., Yim, H. C. H., & Lau, A. S. Y. (2007). Role for nonstructural protein 1 of severe acute respiratory syndrome coronavirus in chemokine dysregulation. *Journal of Virology*, *81*(1), 416–422. https://doi.org/10.1128/JVI.02336-05.

Lee, P., Goishi, K., Davidson Alan, J., Mannix, R., Zon, L., & Klagsbrun, M. (2002). Neuropilin-1 is required for vascular development and is a mediator of VEGF-dependent angiogenesis in zebrafish. *Proceedings of the National Academy of Sciences*, *99*(16), 10470–10475. https://doi.org/10.1073/pnas.162366299.

Lehmann, M., Allers, K., Heldt, C., Meinhardt, J., Schmidt, F., Rodriguez-Sillke, Y., et al. (2021). Human small intestinal infection by SARS-CoV-2 is characterized by a mucosal infiltration with activated CD8+ T cells. *Mucosal Immunology*, *14*(6), 1381–1392. https://doi.org/10.1038/s41385-021-00437-z.

Li, F., Li, J., Wang, P.-H., Yang, N., Huang, J., Ou, J., et al. (2021). SARS-CoV-2 spike promotes inflammation and apoptosis through autophagy by ROS-suppressed PI3K/AKT/mTOR signaling. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, *1867*(12), 166260. https://doi.org/10.1016/j.bbadis.2021.166260.

Li, J. Y., Liao, C. H., Wang, Q., Tan, Y. J., Luo, R., Qiu, Y., et al. (2020). The ORF6, ORF8 and nucleocapsid proteins of SARS-CoV-2 inhibit type I interferon signaling pathway. *Virus Research*, *286*, 198074. https://doi.org/10.1016/j.virusres.2020.198074.

Lim, S., Bae, J. H., Kwon, H.-S., & Nauck, M. A. (2021). COVID-19 and diabetes mellitus: From pathophysiology to clinical management. *Nature Reviews Endocrinology*, *17*(1), 11–30. https://doi.org/10.1038/s41574-020-00435-4.

Long, B., Brady, W. J., Koyfman, A., & Gottlieb, M. (2020). Cardiovascular complications in COVID-19. *The American Journal of Emergency Medicine*, *38*(7), 1504–1507. https://doi.org/10.1016/j.ajem.2020.04.048.

López-Medina, E., López, P., Hurtado, I. C., Dávalos, D. M., Ramirez, O., Martínez, E., et al. (2021). Effect of ivermectin on time to resolution of symptoms among adults with mild COVID-19: A randomized clinical trial. *JAMA*, *325*(14), 1426–1435. https://doi.org/10.1001/jama.2021.3071.

Magro, C., Mulvey, J. J., Berlin, D., Nuovo, G., Salvatore, S., Harp, J., et al. (2020). Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of five cases. *Translational Research: The Journal of Laboratory and Clinical Medicine*, *220*, 1–13. https://doi.org/10.1016/j.trsl.2020.04.007.

Mahase, E. (2021). Covid-19: Pfizer's paxlovid is 89% effective in patients at risk of serious illness, company reports. *BMJ*, *375*, n2713. https://doi.org/10.1136/bmj.n2713.

Mahmud, N., Weiss, A., Trivedi, C., Yang, Y.-X., Lewis, J., & Khan, N. (2021). Risk of venous thromboembolism among patients with inflammatory bowel disease who contract severe acute respiratory syndrome Coronavirus 2. *Gastroenterology*, *161*(5), 1709–1711.e1701. https://doi.org/10.1053/j.gastro.2021.06.012.

Masters, P. S. (2006). The molecular biology of coronaviruses. *Advances in Virus Research*, *66*, 193–292. https://doi.org/10.1016/s0065-3527(06)66005-3.

Meijnikman, A. S., Bruin, S., Groen, A. K., Nieuwdorp, M., & Herrema, H. (2021). Increased expression of key SARS-CoV-2 entry points in multiple tissues in individuals with NAFLD. *Journal of Hepatology*, *74*(3), 748–749. https://doi.org/10.1016/j.jhep.2020.12.007.

Michot, J. M., Albiges, L., Chaput, N., Saada, V., Pommeret, F., Griscelli, F., et al. (2020). Tocilizumab, an anti-IL-6 receptor antibody, to treat COVID-19-related respiratory failure: A case report. *Annals of Oncology*, *31*(7), 961–964. https://doi.org/10.1016/j.annonc.2020.03.300.

Misiti, F. (2021). SARS-CoV-2 infection and red blood cells: Implications for long term symptoms during exercise. *Sports Medicine and Health Science*, *3*(3), 181–182. https://doi.org/10.1016/j.smhs.2021.07.002.

Mitjà, O., Corbacho-Monné, M., Ubals, M., Alemany, A., Suñer, C., Tebé, C., et al. (2021). A cluster-randomized trial of hydroxychloroquine for prevention of Covid-19. *The New England Journal of Medicine*, *384*(5), 417–427. https://doi.org/10.1056/NEJMoa2021801.

Mountantonakis, S. E., Saleh, M., Fishbein, J., Gandomi, A., Lesser, M., Chelico, J., et al. (2021). Atrial fibrillation is an independent predictor for in-hospital mortality in patients admitted with SARS-CoV-2 infection. *Heart Rhythm*, *18*(4), 501–507. https://doi.org/10.1016/j.hrthm.2021.01.018.

Muñoz, M. C., Burghi, V., Miquet, J. G., Giani, J. F., Banegas, R. D., Toblli, J. E., et al. (2014). Downregulation of the ACE2/Ang-(1–7)/Mas axis in transgenic mice overexpressing GH. *Journal of Endocrinology*, *221*(2), 215–227. https://doi.org/10.1530/JOE-13-0497.

Naydenova, K., Muir Kyle, W., Wu, L.-F., Zhang, Z., Coscia, F., Peet Mathew, J., et al. (2021). Structure of the SARS-CoV-2 RNA-dependent RNA polymerase in the presence of favipiravir-RTP. *Proceedings of the National Academy of Sciences*, *118*(7), e2021946118. https://doi.org/10.1073/pnas.2021946118.

Nieto-Torres, J. L., DeDiego, M. L., Verdiá-Báguena, C., Jimenez-Guardeño, J. M., Regla-Nava, J. A., Fernandez-Delgado, R., et al. (2014). Severe acute respiratory syndrome coronavirus envelope protein ion channel activity promotes virus fitness and pathogenesis. *PLoS Pathogens*, *10*(5), e1004077. https://doi.org/10.1371/journal.ppat.1004077.

Ou, X., Liu, Y., Lei, X., Li, P., Mi, D., Ren, L., et al. (2020). Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. *Nature Communications*, *11*(1), 1620. https://doi.org/10.1038/s41467-020-15562-9.

Oudshoorn, D., Rijs, K., Limpens Ronald, W. A. L., Groen, K., Koster Abraham, J., Snijder Eric, J., Kikkert, M., Bárcena, M., & Denison Mark, R. Expression and cleavage of Middle East Respiratory Syndrome Coronavirus nsp3-4 polyprotein induce the formation of double-membrane vesicles that mimic those associated with coronaviral RNA replication. MBio, 8(6), e01658-e01617. doi:https://doi.org/10.1128/mBio.01658-17.

Padmanabhan, P., Desikan, R., & Dixit, N. M. (2020). Targeting TMPRSS2 and Cathepsin B/L together may be synergistic against SARS-CoV-2 infection. *PLoS Computational Biology*, *16*(12), e1008461. https://doi.org/10.1371/journal.pcbi.1008461.

Pan, P., Shen, M., Yu, Z., Ge, W., Chen, K., Tian, M., et al. (2021). SARS-CoV-2 N protein promotes NLRP3 inflammasome activation to induce hyperinflammation. *Nature Communications*, *12*(1), 4664. https://doi.org/10.1038/s41467-021-25015-6.

Pancer, K., Milewska, A., Owczarek, K., Dabrowska, A., Kowalski, M., Łabaj, P. P., et al. (2020). The SARS-CoV-2 ORF10 is not essential in vitro or in vivo in humans. *PLoS Pathogens*, *16*(12), e1008959. https://doi.org/10.1371/journal.ppat.1008959.

Peacock, T. P., Goldhill, D. H., Zhou, J., Baillon, L., Frise, R., Swann, O. C., et al. (2021). The furin cleavage site in the SARS-CoV-2 spike protein is required for transmission in ferrets. *Nature Microbiology*, *6*(7), 899–909. https://doi.org/10.1038/s41564-021-00908-w.

Peng, Q., Peng, R., Yuan, B., Zhao, J., Wang, M., Wang, X., et al. (2020). Structural and biochemical characterization of the nsp12-nsp7-nsp8 core polymerase complex from SARS-CoV-2. *Cell Reports*, *31*(11), 107774. https://doi.org/10.1016/j.celrep.2020.107774.

Peng, H., Sarwar, Z., Yang, X. P., Peterson, E. L., Xu, J., Janic, B., et al. (2015). Profibrotic role for interleukin-4 in cardiac remodeling and dysfunction. *Hypertension*, *66*(3), 582–589. https://doi.org/10.1161/hypertensionaha.115.05627.

Prakash, J., Mittal, B., Awasthi, S., Agarwal, C. G., & Srivastava, N. (2013). Hypoadiponectinemia in obesity: Association with insulin resistance. *Indian Journal of Clinical Biochemistry: IJCB*, *28*(2), 158–163. https://doi.org/10.1007/s12291-012-0246-3.

Qiao, Y., Wang, X.-M., Mannan, R., Pitchiaya, S., Zhang, Y., Wotring Jesse, W., et al. (2021). Targeting transcriptional regulation of SARS-CoV-2 entry factors ACE2 and TMPRSS2. *Proceedings of the National Academy of Sciences*, *118*(1), e2021450118. https://doi.org/10.1073/pnas.2021450118.

Rajendran, P., Rengarajan, T., Thangavel, J., Nishigaki, Y., Sakthisekaran, D., Sethi, G., et al. (2013). The vascular endothelium and human diseases. *International Journal of Biological Sciences*, *9*(10), 1057–1069. https://doi.org/10.7150/ijbs.7502.

Rashid, F., Dzakah, E. E., Wang, H., & Tang, S. (2021). The ORF8 protein of SARS-CoV-2 induced endoplasmic reticulum stress and mediated immune evasion by antagonizing production of interferon beta. *Virus Research*, *296*, 198350. https://doi.org/10.1016/j.virusres.2021.198350.

Redondo, N., Zaldívar-López, S., Garrido, J. J., & Montoya, M. (2021). SARS-CoV-2 accessory proteins in viral pathogenesis: Knowns and unknowns [mini review]. *Frontiers in Immunology*, *12*. https://doi.org/10.3389/fimmu.2021.708264.

Reynolds, H. R., Adhikari, S., Pulgarin, C., Troxel, A. B., Iturrate, E., Johnson, S. B., et al. (2020). Renin–angiotensin–aldosterone system inhibitors and risk of Covid-19. *New England Journal of Medicine*, *382*(25), 2441–2448. https://doi.org/10.1056/NEJMoa2008975.

Richardson, P., Griffin, I., Tucker, C., Smith, D., Oechsle, O., Phelan, A., et al. (2020). Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *Lancet (London, England)*, *395*(10223), e30–e31. https://doi.org/10.1016/S0140-6736(20)30304-4.

Robles, J. P., Zamora, M., Adan-Castro, E., Siqueiros-Marquez, L., Martinez de la Escalera, G., & Clapp, C. (2022). The spike protein of SARS-CoV-2 induces endothelial inflammation through integrin α5β1 and NF-κB signaling. *The Journal of Biological Chemistry*, *101695*. https://doi.org/10.1016/j.jbc.2022.101695.

Ruiz-Ares, G., Jimenez-Valero, S., Fernández-Prieto, A., Arbas-Redondo, E., Díaz-Pollán, B., Navia, P., et al. (2021). Concurrent stroke and myocardial infarction after mild COVID-19 infection. *The Neurologist*, *26*(3), 86–89. https://doi.org/10.1097/NRL.0000000000000311.

Sarin, S. K., Choudhury, A., Lau, G. K., Zheng, M.-H., Ji, D., Abd-Elsalam, S., et al. (2020). Pre-existing liver disease is associated with poor outcome in patients with SARS CoV2 infection: The APCOLIS Study (APASL COVID-19 Liver Injury Spectrum Study). *Hepatology International*, *14*(5), 690–700. https://doi.org/10.1007/s12072-020-10072-8.

Sartorius, R., Trovato, M., Manco, R., D'Apice, L., & De Berardinis, P. (2021). Exploiting viral sensing mediated by Toll-like receptors to design innovative vaccines. *NPJ Vaccines*, *6*(1), 127. https://doi.org/10.1038/s41541-021-00391-8.

Schaffner, F., Ray, A. M., & Dontenwill, M. (2013). Integrin α5β1, the fibronectin receptor, as a pertinent therapeutic target in solid tumors. *Cancers*, *5*(1), 27–47. https://doi.org/10.3390/cancers5010027.

Schoeman, D., & Fielding, B. C. (2019). Coronavirus envelope protein: Current knowledge. *Virology Journal*, *16*(1), 69. https://doi.org/10.1186/s12985-019-1182-0.

Sharma, B. R., & Kanneganti, T.-D. (2021). NLRP3 inflammasome in cancer and metabolic diseases. *Nature Immunology*, *22*(5), 550–559. https://doi.org/10.1038/s41590-021-00886-5.

Shchendrygina, A., Nagel, E., Puntmann, V. O., & Valbuena-Lopez, S. (2021). COVID-19 myocarditis and prospective heart failure burden. *Expert Review of Cardiovascular Therapy*, *19*(1), 5–14. https://doi.org/10.1080/14779072.2021.1844005.

Shen, L. W., Mao, H. J., Wu, Y. L., Tanaka, Y., & Zhang, W. (2017). TMPRSS2: A potential target for treatment of influenza virus and coronavirus infections. *Biochimie*, *142*, 1–10. https://doi.org/10.1016/j.biochi.2017.07.016.

Shi, C.-S., Qi, H.-Y., Boularan, C., Huang, N.-N., Abu-Asab, M., Shelhamer, J. H., et al. (2014). SARS-coronavirus open reading frame-9b suppresses innate immunity by targeting mitochondria and the MAVS/TRAF3/TRAF6 signalosome. *Journal of Immunology (Baltimore, Md.: 1950)*, *193*(6), 3080–3089. https://doi.org/10.4049/jimmunol.1303196.

Shi, J.-H., & Sun, S.-C. (2018). Tumor necrosis factor receptor-associated factor regulation of nuclear factor κB and mitogen-activated protein kinase pathways [review]. *Frontiers in Immunology*, *9*. https://doi.org/10.3389/fimmu.2018.01849.

Shilts, J., Crozier, T. W. M., Greenwood, E. J. D., Lehner, P. J., & Wright, G. J. (2021). No evidence for basigin/CD147 as a direct SARS-CoV-2 spike binding receptor. *Scientific Reports*, *11*(1), 413. https://doi.org/10.1038/s41598-020-80464-1.

Siu, K.-L., Yuen, K.-S., Castano-Rodriguez, C., Ye, Z.-W., Yeung, M.-L., Fung, S.-Y., et al. (2019). Severe acute respiratory syndrome Coronavirus ORF3a protein activates the NLRP3 inflammasome by promoting TRAF3-dependent ubiquitination of ASC. *The FASEB Journal*, *33*(8), 8865–8877. https://doi.org/10.1096/fj.201802418R.

Smith, E. C., Blanc, H., Vignuzzi, M., & Denison, M. R. (2013). Coronaviruses lacking exoribonuclease activity are susceptible to lethal mutagenesis: Evidence for proofreading and potential therapeutics. *PLoS Pathogens*, *9*(8), e1003565. https://doi.org/10.1371/journal.ppat.1003565.

Sola, I., Almazán, F., Zúñiga, S., & Enjuanes, L. (2015). Continuous and discontinuous RNA synthesis in coronaviruses. *Annual Review of Virology*, *2*(1), 265–288. https://doi.org/10.1146/annurev-virology-100114-055218.

Song, P., Li, W., Xie, J., Hou, Y., & You, C. (2020). Cytokine storm induced by SARS-CoV-2. *Clinica Chimica Acta*, *509*, 280–287. https://doi.org/10.1016/j.cca.2020.06.017.

Stefan, N., & Häring, H.-U. (2013). The role of hepatokines in metabolism. *Nature Reviews Endocrinology*, *9*(3), 144–152. https://doi.org/10.1038/nrendo.2012.258.

Su, Q., Tsai, J., Xu, E., Qiu, W., Bereczki, E., Santha, M., et al. (2009). Apolipoprotein B100 acts as a molecular link between lipid-induced endoplasmic reticulum stress and hepatic insulin resistance. *Hepatology*, *50*(1), 77–84. https://doi.org/10.1002/hep.22960.

Su, Q., Wang, S., Baltzis, D., Qu, L.-K., Wong Andrew, H.-T., & Koromilas Antonis, E. (2006). Tyrosine phosphorylation acts as a molecular switch to full-scale activation of the eIF2α RNA-dependent protein kinase. *Proceedings of the National Academy of Sciences*, *103*(1), 63–68. https://doi.org/10.1073/pnas.0508207103.

Tam, B. T., Morais, J. A., & Santosa, S. (2020). Obesity and ageing: Two sides of the same coin. *Obesity Reviews*, *21*(4), e12991. https://doi.org/10.1111/obr.12991.

Tang, T., Bidon, M., Jaimes, J. A., Whittaker, G. R., & Daniel, S. (2020). Coronavirus membrane fusion mechanism offers a potential target for antiviral development. *Antiviral Research*, *178*, 104792. https://doi.org/10.1016/j.antiviral.2020.104792.

Targher, G., Mantovani, A., Byrne, C. D., Wang, X.-B., Yan, H.-D., Sun, Q.-F., et al. (2020). Risk of severe illness from COVID-19 in patients with metabolic dysfunction-associated fatty liver disease and increased fibrosis scores. *Gut*, *69*(8), 1545. https://doi.org/10.1136/gutjnl-2020-321611.

Thomas, S. (2020). The structure of the membrane protein of SARS-CoV-2 resembles the sugar transporter SemiSWEET. *Pathogens & Immunity*, *5*(1), 342–363. https://doi.org/10.20411/pai.v5i1.377.

Thum, T. (2020). SARS-CoV-2 receptor ACE2 expression in the human heart: Cause of a post-pandemic wave of heart failure? *European Heart Journal*, *41*(19), 1807–1809. https://doi.org/10.1093/eurheartj/ehaa410.

Trypsteen, W., Van Cleemput, J., Snippenberg, W. V., Gerlo, S., & Vandekerckhove, L. (2020). On the whereabouts of SARS-CoV-2 in the human body: A systematic review. *PLoS Pathogens*, *16*(10), e1009037. https://doi.org/10.1371/journal.ppat.1009037.

Tudoran, C., Tudoran, M., Lazureanu, V. E., Marinescu, A. R., Pop, G. N., Pescariu, A. S., et al. (2021). Evidence of pulmonary hypertension after SARS-CoV-2 infection in subjects without previous significant cardiovascular pathology. *Journal of Clinical Medicine*, *10*(2). https://doi.org/10.3390/jcm10020199.

Ulasli, M., Verheije, M. H., de Haan, C. A., & Reggiori, F. (2010). Qualitative and quantitative ultrastructural analysis of the membrane rearrangements induced by coronavirus. *Cellular Microbiology*, *12*(6), 844–861. https://doi.org/10.1111/j.1462-5822.2010.01437.x.

V'kovski, P., Kratzel, A., Steiner, S., Stalder, H., & Thiel, V. (2021). Coronavirus biology and replication: Implications for SARS-CoV-2. *Nature Reviews Microbiology*, *19*(3), 155–170. https://doi.org/10.1038/s41579-020-00468-6.

Valcarcel, A., Bensussen, A., Álvarez-Buylla, E. R., & Díaz, J. (2021). Structural analysis of SARS-CoV-2 ORF8 protein: Pathogenic and therapeutic implications [mini review]. *Frontiers in Genetics*, *12*. https://doi.org/10.3389/fgene.2021.693227.

Vankadari, N. (2020). Structure of furin protease binding to SARS-CoV-2 spike glycoprotein and implications for potential targets and virulence. *The Journal of Physical Chemistry Letters*, *11*(16), 6655–6663. https://doi.org/10.1021/acs.jpclett.0c01698.

Verdecchia, P., Cavallini, C., Spanevello, A., & Angeli, F. (2020). The pivotal link between ACE2 deficiency and SARS-CoV-2 infection. *European Journal of Internal Medicine*, *76*, 14–20. https://doi.org/10.1016/j.ejim.2020.04.037.

Vidak, E., Javoršek, U., Vizovišek, M., & Turk, B. (2019). Cysteine cathepsins and their extracellular roles: Shaping the microenvironment. *Cell*, *8*(3), 264. https://doi.org/10.3390/cells8030264.

Viswanathan, T., Arya, S., Chan, S.-H., Qi, S., Dai, N., Misra, A., et al. (2020). Structural basis of RNA cap modification by SARS-CoV-2. *Nature Communications*, *11*(1), 3718. https://doi.org/10.1038/s41467-020-17496-8.

Vithani, N., Ward, M. D., Zimmerman, M. I., Novak, B., Borowsky, J. H., Singh, S., et al. (2021). SARS-CoV-2 Nsp 16 activation mechanism and a cryptic pocket with pan-coronavirus antiviral potential. *Biophysical Journal*, *120*(14), 2880–2889. https://doi.org/10.1016/j.bpj.2021.03.024.

Wambier, C. G., & Goren, A. (2020). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is likely to be androgen mediated. *Journal of the American Academy of Dermatology*, *83*(1), 308–309. https://doi.org/10.1016/j.jaad.2020.04.032.

Wang, K., Chen, W., Zhang, Z., Deng, Y., Lian, J.-Q., Du, P., et al. (2020). CD147-spike protein is a novel route for SARS-CoV-2 infection to host cells. *Signal Transduction and Targeted Therapy*, *5*(1), 283. https://doi.org/10.1038/s41392-020-00426-x.

Wang, K., Chen, W., Zhou, Y.-S., Lian, J.-Q., Zhang, Z., Du, P., et al. (2020). SARS-CoV-2 invades host cells via a novel route: CD147-spike protein. *bioRxiv*. https://doi.org/10.1101/2020.03.14.988345. 2020.2003.2014.988345.

Wang, H., Quirion, R., Little, P. J., Cheng, Y., Feng, Z. P., Sun, H. S., et al. (2015). Forkhead box O transcription factors as possible mediators in the development of major depression. *Neuropharmacology*, *99*, 527–537. https://doi.org/10.1016/j.neuropharm.2015.08.020.

Whittaker, G. R. (2021). SARS-CoV-2 spike and its adaptable furin cleavage site. *The Lancet Microbe*, *2*(10), e488–e489. https://doi.org/10.1016/S2666-5247(21)00174-9.

Wolff, G., Limpens, R., Zevenhoven-Dobbe, J. C., Laugks, U., Zheng, S., de Jong, A. W. M., et al. (2020). A molecular pore spans the double membrane of the coronavirus replication organelle. *Science*, *369*(6509), 1395–1398. https://doi.org/10.1126/science.abd3629.

Wu, C.-H., Mohammadmoradi, S., Chen, J. Z., Sawada, H., Daugherty, A., & Lu, H. S. (2018). Renin-angiotensin system and cardiovascular functions. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *38*(7), e108–e116. https://doi.org/10.1161/ATVBAHA.118.311282.

Wu, X., Sun, Z., Trzeciakowski, J. P., Meininger, G. A., & Muthuchamy, M. (2006). Abstract 536: Mechanical properties of the interaction between fibronectin and α5β1-integrin on cardiomyocytes studied by atomic force microscopy. *Circulation*, *114*(Suppl. 18), II_84. https://doi.org/10.1161/circ.114.suppl_18.II_84.

Xia, H., Cao, Z., Xie, X., Zhang, X., Chen, J. Y., Wang, H., et al. (2020). Evasion of Type I Interferon by SARS-CoV-2. *Cell Reports*, *33*(1), 108234. https://doi.org/10.1016/j.celrep.2020.108234.

Xia, S., Zhu, Y., Liu, M., Lan, Q., Xu, W., Wu, Y., et al. (2020). Fusion mechanism of 2019-nCoV and fusion inhibitors targeting HR1 domain in spike protein. *Cellular & Molecular Immunology*, *17*(7), 765–767. https://doi.org/10.1038/s41423-020-0374-2.

Xu, J., Fan, J., Wu, F., Huang, Q., Guo, M., Lv, Z., et al. (2017). The ACE2/angiotensin-(1–7)/Mas receptor axis: Pleiotropic roles in cancer [review]. *Frontiers in Physiology*, *8*. https://doi.org/10.3389/fphys.2017.00276.

Yang, L., Nilsson-Payant, B. E., Han, Y., Jaffré, F., Zhu, J., Wang, P., et al. (2021). Cardiomyocytes recruit monocytes upon SARS-CoV-2 infection by secreting CCL2. *Stem Cell Reports*, *16*(9), 2274–2288. https://doi.org/10.1016/j.stemcr.2021.07.012.

Yang, J., Petitjean, S. J. L., Koehler, M., Zhang, Q., Dumitru, A. C., Chen, W., et al. (2020). Molecular interaction and inhibition of SARS-CoV-2 binding to the ACE2 receptor. *Nature Communications*, *11*(1), 4541. https://doi.org/10.1038/s41467-020-18319-6.

Yang, R., Zhao, Q., Rao, J., Zeng, F., Yuan, S., Ji, M., et al. (2021). SARS-CoV-2 accessory protein ORF7b mediates tumor necrosis factor-α-induced apoptosis in cells [original research]. *Frontiers in Microbiology*, *12*. https://doi.org/10.3389/fmicb.2021.654709.

Ye, Q., Lu, S., & Corbett, K. D. (2021). Structural basis for SARS-CoV-2 nucleocapsid protein recognition by single-domain antibodies [original research]. *Frontiers in Immunology*, *12*. https://doi.org/10.3389/fimmu.2021.719037.

Ye, J., Zhang, B., Xu, J., Chang, Q., McNutt, M. A., Korteweg, C., et al. (2007). Molecular pathology in the lungs of severe acute respiratory syndrome patients. *The American Journal of Pathology*, *170*(2), 538–545. https://doi.org/10.2353/ajpath.2007.060469.

Yelland, T., & Djordjevic, S. (2016). Crystal structure of the neuropilin-1 MAM domain: Completing the neuropilin-1 ectodomain picture. *Structure (London, England: 1993)*, *24*(11), 2008–2015. https://doi.org/10.1016/j.str.2016.08.017.

Yu, C. J., Chen, Y. C., Hsiao, C. H., Kuo, T. C., Chang, S. C., Lu, C. Y., et al. (2004). Identification of a novel protein 3a from severe acute respiratory syndrome coronavirus. *FEBS Letters*, *565*(1-3), 111–116. https://doi.org/10.1016/j.febslet.2004.03.086.

Yuan, X., Li, J., Shan, Y., Yang, Z., Zhao, Z., Chen, B., et al. (2005). Subcellular localization and membrane association of SARS-CoV 3a protein. *Virus Research*, *109*(2), 191–202. https://doi.org/10.1016/j.virusres.2005.01.001.

Zamorano Cuervo, N., & Grandvaux, N. (2020). ACE2: Evidence of role as entry receptor for SARS-CoV-2 and implications in comorbidities. *eLife*, *9*, e61390. https://doi.org/10.7554/eLife.61390.

Zhang, J. Z., Liu, Z., Liu, J., Ren, J. X., & Sun, T. S. (2014). Mitochondrial DNA induces inflammation and increases TLR9/NF-κB expression in lung tissue. *International Journal of Molecular Medicine*, *33*(4), 817–824. https://doi.org/10.3892/ijmm.2014.1650.

Zhang, K., Miorin, L., Makio, T., Dehghan, I., Gao, S., Xie, Y., et al. (2021). Nsp1 protein of SARS-CoV-2 disrupts the mRNA export machinery to inhibit host gene expression. *Science Advances*, *7*(6), eabe7386. https://doi.org/10.1126/sciadv.abe7386.

Zhao, H., Lu, L., Peng, Z., Chen, L.-L., Meng, X., Zhang, C., et al. (2022). SARS-CoV-2 Omicron variant shows less efficient replication and fusion activity when compared with Delta variant in TMPRSS2-expressed cells. *Emerging Microbes & Infections*, *11*(1), 277–283. https://doi.org/10.1080/22221751.2021.2023329.

Zhao, M.-M., Yang, W.-L., Yang, F.-Y., Zhang, L., Huang, W.-J., Hou, W., et al. (2021). Cathepsin L plays a key role in SARS-CoV-2 infection in humans and humanized mice and is a promising target for new drug development. *Signal Transduction and Targeted Therapy*, *6*(1), 134. https://doi.org/10.1038/s41392-021-00558-8.

Zhong, J., Basu, R., Guo, D., Chow, F. L., Byrns, S., Schuster, M., et al. (2010). Angiotensin-converting enzyme 2 suppresses pathological hypertrophy, myocardial fibrosis, and cardiac dysfunction. *Circulation*, *122*(7), 717–728. https://doi.org/10.1161/CIRCULATIONAHA.110.955369.

Zhong, F.-Y., Zhao, Y.-C., Zhao, C.-X., Gu, Z.-C., Lu, X.-Y., Jiang, W.-L., et al. (2022). The role of CD147 in pathological cardiac hypertrophy is regulated by glycosylation. *Oxidative Medicine and Cellular Longevity*, *2022*, 6603296. https://doi.org/10.1155/2022/6603296.

Zhou, Y., Frey, T. K., & Yang, J. J. (2009). Viral calciomics: Interplays between Ca2+ and virus. *Cell Calcium*, *46*(1), 1–17. https://doi.org/10.1016/j.ceca.2009.05.005.

Zhou, Z., Huang, C., Zhou, Z., Huang, Z., Su, L., Kang, S., et al. (2021). Structural insight reveals SARS-CoV-2 ORF7a as an immunomodulating factor for human CD14(+) monocytes. *iScience*, *24*(3), 102187. https://doi.org/10.1016/j.isci.2021.102187.

Zizzo, M. G., Auteri, M., Amato, A., Caldara, G., Nuzzo, D., Di Carlo, M., et al. (2017). Angiotensin II type II receptors and colonic dysmotility in 2,4-dinitrofluorobenzenesulfonic acid-induced colitis in rats. *Neurogastroenterology and Motility*, *29*(6). https://doi.org/10.1111/nmo.13019.