COVID-19 and Crosstalk With the Hallmarks of Aging

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Abstract

Within the past several decades, the emergence of new viral diseases with severe health complications and mortality is evidence of an age-dependent, compromised bodily response to abrupt stress with concomitantly reduced immunity. The new severe acute respiratory syndrome coronavirus 2, SARS-CoV-2, causes coronavirus disease 2019 (COVID-19). It has increased morbidity and mortality in persons with underlying chronic diseases and those with a compromised immune system regardless of age and in older adults who are more likely to have these conditions. While SARS-CoV-2 is highly virulent, there is variability in the severity of the disease and its complications in humans. Severe pneumonia, acute respiratory distress syndrome, lung fibrosis, cardiovascular events, acute kidney injury, stroke, hospitalization, and mortality have been reported that result from pathogen–host interactions. Hallmarks of aging, interacting with one another, have been proposed to influence health span in older adults, possibly via mechanisms regulating the immune system. Here, we review the potential roles of the hallmarks of aging coupled with host–coronavirus interactions. Of these hallmarks, we focused on those that directly or indirectly interact with viral infections, including immunosenescence, inflammation and inflammasomes, adaptive immunosenescence, genomic instability, mitochondrial dysfunction, telomere attrition, epigenetic alterations, and impaired autophagy. These hallmarks likely contribute to the increased pathophysiological responses to SARS-CoV-2 among older adults and may play roles as an additive risk of accelerated biological aging even after recovery. We also briefly discuss the role of anti-aging drug candidates that require paramount attention in COVID-19 research.

Keywords: COVID-19, pandemic, comorbidity, aging, hallmarks of aging, anti-aging

Introduction

The recently emerged severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is distinguished phylogenetically from other coronaviruses (1), causing more severe upper respiratory tract infections, respiratory distress, and hospitalization. These symptoms often result in admissions to intensive care units (ICUs), mechanical ventilation, as well as mortality (2, 3), mainly in persons with compromised immune systems and/or comorbidities such as diabetes, hypertension, and cancer (4). Previous outbreaks of community-acquired pneumonia and severe respiratory disease from coronaviruses reported in 2003 and 2012 were caused by SARSCoV-1 and the Middle East respiratory syndrome (MERS-CoV), respectively (5). The latest coronavirus disease 2019 (COVID-19) started in Wuhan, China (6), and with its high virulence capacity and fast transmissibility, primarily through aerosol droplets (7), rapidly spread around the world. COVID-19 can be asymptomatic or minimally symptomatic with or without fever, cough, shortness of breath, fatigue, and gastrointestinal symptoms. COVID-19 can progress to moderate or severe pneumonia, severe symptomatic acute respiratory distress syndrome (ARDS), cardiovascular complications, kidney injury, stroke, and mortality (2, 4, 8, 9). In laboratory examinations, most patients appeared to have "cytokine storm," leukopenia, thrombocytopenia, and coagulopathy (2, 10). Computed tomography depicted multifocal ground-glass opacities and subsegmental areas of consolidation and fibrosis—in some cases even without overt clinical symptoms (11).

The silent spread of SARS-CoV-2 via asymptomatic cases likely increases transmission to all individuals, especially to older persons who are at higher risk for more severe complications (3) or abruptly develop stroke or cardiovascular incidents as the result of virus–host interactions.

Therefore, understanding the variability in host responses to viral infection is likely to yield better clinical management among older adults (12, 13).

Normal aging includes changes at the cell, tissue, and organ levels (hallmarks of aging) that are known to contribute to morbidity, frailty, and mortality in the aging population. Hallmarks of aging impact all aspects of cellular and system functions (14, 15). Some hallmarks interact directly or indirectly with viral infection; examples include genomic instability, telomere attrition, impaired autophagy, mitochondrial dysfunction, innate immunosenescence, inflammation and inflammasomes, adaptive immunosenescence, and epigenetic alterations that result in variability in reserve and adaptation capacity in response to stress. The hallmarks of aging impact one another and play roles in chronic diseases (14–16). With the COVID-19 pandemic, consideration of these hallmarks when treating infected older patients may be critical to enhance positive outcomes (12, 13). Here, we focus on some of the hallmarks of aging with regard to their potential roles in the host response to SARS-CoV-2 infection (Figure 1) and as possible underlying factors for poorer outcomes.

SARS-CoV-2 virology

Classified within the *Coronaviridae* family, SARS-CoV-2 shares the main common characteristics of this family. Coronaviruses are enveloped with large (~30-kb) single-stranded positive-sense RNA (17). Their genome is divided into two parts, 5` two-thirds and 3` one-third, with the former including open reading frames (ORF1a and ORF1b) that encode pp1a and pp1ab, two large polyproteins that can be cleaved to nonstructural proteins (nsp1 to 16) required for the synthesis of new viral genetic material. The rest of the genome includes genes that encode the structural proteins to produce virions and accessory genes that play a role in the host response (17).

Structural proteins include the spike (S) glycoprotein, known for its pathogenicity, that comprises two functional subunits: S1 as the receptor-binding domain and S2 that mediates fusion between the virus envelope and host cell membrane. Other coronavirus proteins include nucleocapsid (N), involved in genome replication; a membrane (M) protein from the host endoplasmic reticulum (ER) or Golgi responsible for virus assembly; and the envelope protein (E) (Figure 2, Table1). SARS-CoV-2 highly resembles SARS-CoV-1, sharing 77% similarity with the residual amino acids of the S protein (1). Also, the similarity of N, M, and 3a proteins in SARS-CoV-1 and SARS-CoV-2 implies a similar pathogenic pathway. SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2), a cell surface receptor that converts the vasopressor octapeptide angiotensin-II to the vasodilator angiotensin1-7 and is highly expressed in the vascular endothelia, lung, kidney, small intestine epithelial cells, immune cells, and testis (18, 19). Following binding to ACE2, the virus enters the cell through either an endosome (in acidic environments) or by host cell protease cleavage, such as TMPRSS2 and furin (20–22). Using their own RNA polymerase, coronaviruses replicate their genome in the host cell cytoplasm and employ the host ribosome machinery to produce proteins. Subsequent viral assembly occurs in the host endoplasmic reticulum–Golgi intermediate complex (ERGIC) and mature virions are released through a secretory mechanism in smooth-walled vesicles, resulting in ER stress (Figure 2).

Hallmarks of Aging and COVID-19

Innate immunosenescence, inflammation, and inflammasomes

The human body uses pattern recognition receptors (PRRs) to identify pathogen-associated molecular patterns (PAMPs) and endogenous danger (or damage)-associated molecular patterns (DAMPs). The most well-known PRRs include the Toll-like receptors (TLRs), cytoplasmic

retinoic acid-inducible gene-I (RIG-I), the RIG-I-like receptor (RLR), and the nucleotide-binding

oligomerization domain-like receptor (NLR). TLRs such as TLR7 are induced in response to

recognized particles (23, 24), including single-stranded RNA viruses, and stimulate

proinflammatory cytokines and interferons (IFNs) type I and III (25). The latter, released from

virus-infected cells, upregulates IFN-stimulated genes, which is a first step in limiting viral entry

or viral replication (26). At later stages, IFNs can inhibit viral assembly, the viral spread, and

modulate the immune system by promoting macrophage, NK, T, and B cell activities (27). It has

been suggested that coronavirus can antagonize IFNs and thereby evade the immune system (28).

RIG-I-like receptors, which reside on mitochondria, can detect RNA viruses and activate

mitochondrial antiviral-signaling proteins (MAVS). MAVS, in turn, increase proinflammatory

cytokines including interleukin (IL)-6, tumor necrosis factor-α (TNF-α) that are related to

nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway

, interferon regulatory factors (IRFs), and inflammasome-related cytokines (IL-1β and IL-18)

(23). Elevated inflammasome pathways in normal aging have been associated with age-related

chronic diseases (29, 30). By further stimulating inflammasome pathway activity, viral infections

can exacerbate age-related impairment of immunological responses. With aging, the decline in

innate immunity attenuates interferon responses to viral infection in neutrophils, monocytes and

macrophages, and NK cells (24, 27, 31, 32). Moreover, costimulatory signals are reduced from

the antigen-presenting cells (APCs) including macrophages, B cells, NK, and dendritic cells that

are required to activate T cells (32).

Coronaviruses have been shown to activate both the NLRP3 inflammasome and the NF-κB

pathway (33, 34). Of particular importance are elevated levels of tumor necrosis factor-alpha

(TNF-α) converting enzyme (TACE), a proteolytic enzyme in the processing of TNF-α, TNF

receptors (TNFRs), and ACE2. Both ACE2 and TACE levels are associated with poor prognosis in heart failure. In addition, TNFR-1 and TNFR-2 are strongly associated with kidney failure in older adults (35). ACE2 is an enzyme that promotes the formation of angiotensin 1-7, which has anti-inflammatory functions (36-38). However, ACE2 expression levels in human aging and ACE2 activity upon SARS-CoV-2 infection remain to be elucidated.

Moreover, in response to viral infections, plasminogen-activator inhibitor-1 (PAI-1) level increases to neutralize proteases such as TMPRSS2 and thus reduces the infectivity. Transforming growth factor-beta (TGF-beta) increases in response to persistent inflammation, and is known to trigger SERPINE1 expression, the gene encoding PAI-1, which further increases TGF-beta levels (26). Of note, increased PAI-1 level, a known marker of senescence (39), may increase thromboembolism and coagulopathy, which are risk factors for acute cardiovascular events and stroke (26). Similar to MESR-CoV, SARS-CoV-2 also has been reported to have a furin-like cleavage site (40). Furin, another host cell protease, stimulates both NLRP3 and NF-κB inflammatory pathways, and activates TGF-beta (41). Notably, TGF-beta and growth differentiation factor 15 (GDF15), a member of TGF-beta superfamily, are known markers associated with aging (42) as well as significant prognostic markers in ARDS (43, 44).

Adaptive immunosenescence

Adaptive immunity that identifies and responds to specific pathogens includes humoral and cellular immunities, which are mediated by B cells, and CD8^{+} and CD4^{+} T cells, respectively. B lymphocytes are triggered to differentiate into immunoglobin-producing plasma cells by cytokine production from CD4^{+} cells (42). Increased levels of all immunoglobulins (Ig), including IgA from respiratory mucosal cells, IgM, and IgG, have been reported in response to coronavirus (23). IgM is the first antibody secreted in response to acute viral infection. IgG,

produced later and enhanced upon reinfection, facilitates phagocytosis of infected cells and antibody-dependent cellular toxicity by both NK and CD8^{+} cells (45). With aging, there is a shift from the naïve toward memory B cells, alterations in the key stimulatory factors mediating the B cell response to antigens, as well as reduced capacity for antigen recognition sites on antibodies to recognize novel pathogens. Moreover, in response to antiviral vaccines, long-lived plasma cells decrease (46).

With aging, in addition to the decreased number of naïve T cells, communication between T cells and APC cells, which is required to convert naïve T cells to memory cells, is reduced (47). Upon viral infection, the activated cytotoxic CD8^{+} cells release the lysing enzymes to degrade infected cells and viral genomes. If CD8^{+} cells fail to eliminate the virus, cytokines released from CD4^{+} T effector cells induce augmented inflammatory responses (48). Decreased numbers of naïve CD8^{+} T cells and reduced T cell receptor (TCR) diversity—as well as alterations in distribution and function of effector, memory, and regulatory CD8^{+} T cells—lead to impaired recognition of new antigens and accumulation of dysfunctional memory T cells (49–51). Of note, transcription factor FOXO3 that is expressed on T cells was shown to play an essential role in the regulation of T cell functions in response to pathogens (52).

Notably, age-dependent sex-discrepancy in immune systems has been demonstrated (53) and the incidence of coronavirus infection has also been reported to be higher in men than women. With SARS-CoV-1, viral titers and the accumulation of inflammatory monocytes and neutrophils in the lungs were higher among men than women (54, 55). A study of epigenomics and transcriptomics of immune cells has suggested a bimodal reduction in B cell function in men, first in the early 30s and then at age 65 years and older (53). The sex- and age-dependent immune cell-specific epigenetic and transcriptomic discrepancy can also underlie the sex and age

differences in severity of COVID-19 symptoms. Moreover, estrogen receptor signaling (56), variability in testosterone levels, and androgen receptor expression have been implicated in the variability of immune responses (57). Notably, androgen receptor element genes are upstream to the TMPRSS2 transcription start site and regulate its expression (58). While more rigorous epidemiological data on sex and age distribution of COVID-19 are warranted (59), more investigation on sex- and age-dependent immune response to RNA viral infections will shed more light on reported COVID-19 severity.

DNA repair and genomic instability

The accumulation of somatic mutations, genomic instability, and attenuated DNA repair have been shown in aging immune cells. The overexpression of oxidative stress seen with a viral infection, along with attenuated DNA repair capacity, could accelerate genome instability and apoptosis in non-infected cells (60, 61).

Among DNA repair mechanisms, p53 plays a vital role in response to low levels of stress and protects cells from oxidative damage. Conversely, higher levels of oxidative stress (e.g., increased inflammatory responses secondary to viral infection) result in persistent activation of p53 and increased mitochondrial outer membrane permeability, which in turn leads to apoptosis (Figure 2) (62). Although p53 can downregulate coronavirus replication via regulation of the cell cycle (63), the coronavirus papain-like protease degrades p53 and allows replication of infected cells (64). Further, the DNA damage response (DDR) can play a role in the pathogenesis of RNA viruses through induction of apoptosis, deleterious somatic mutations, and excessive stimulation of inflammatory immune responses (Figure 3) (65). Additionally, coronavirus can inhibit the activity of the cyclin-dependent protein complex, resulting in inactivation of the retinoblastoma protein, which is an important tumor suppressor protein and cell cycle check (66).

Of note, coronavirus accessory proteins such as the 7a protein also mediate apoptosis by interfering with Bcl-X (an antiapoptotic protein); additionally, coronavirus accessory proteins 3a and 9b, as well as structural proteins such as S, E, M, and N modulate apoptosis by inducing ER stress and activating the p38 MAPK pathway (Figure 2) (67, 68).

Collectively, adverse cellular responses to DNA damage and diminished DNA repair capacity have been associated with genome instability and a decline in immune system function. This hallmark of aging not only is likely to be a risk for poor outcomes in older adults but also is likely to be amplified by coronavirus infection.

Mitochondrial dysfunction

Mitochondria, through several functions, play pivotal roles in cell homeostasis. They play a powerhouse role with metabolic oxidation via the tricarboxylic acid cycle and the production of adenosine triphosphate (ATP) via the electron transport chain, and the beta-oxidation of fatty acids. With aging, mitochondrial phosphorylation capacity is decreased. Accordingly, the increased energy expenditure secondary to a cytokine storm can lead to a nonadaptive state, overwhelming the metabolic reserve capacity of mitochondria among older adults who have COVID-19. As a normal body function against pathogens, mitochondria also produce reactive oxygen species (ROS) (69). However, excessive ROS production can be damaging in a similar way to encountering coronavirus infection (70). Moreover, augmented ROS production, known as one of the contemporary theories of aging, has been associated with age-related diseases and decreased life span (71). Though diminished with aging, detoxifying systems including catalase, superoxide dismutase, glutathione peroxidase and glutathione reductase with selenium and magnesium as their cofactors (72), vitamins E and C, and coenzyme Q10 (CoQ10) all help inimize ROS-induced tissue damage (73). Supplementation with CoQ10, an integral part of the

mitochondrial respiratory chain, has been linked with antioxidant activity, less severe respiratory viral infections, and less severe inflammatory response (74).

As mentioned above, mitochondria regulate innate and adaptive immunity (e.g., viral RNA activates MAVS via RIG-I on mitochondria), which in turn stimulate NF-κB, NLRP3 pathways, and interferon-regulatory factors. Mitochondria also mediate cytotoxic responses to lung cell stress (75, 76).

Together, the combination of impaired respiration, diminished ATP production, increased ROS, and reduced detoxification capacity with dysregulated immune functions seems likely to play a pivotal role in the increased inflammation and severity of COVID-19.

Epigenetic alterations

With aging, epigenomic alterations play a pivotal role in distinguishing immune cell phenotypes and regulating inflammatory responses to intrinsic or extrinsic stressors. Age is one of the main drivers of variations in chromatin structure measured by the assay for transposase-accessible chromatin with high-throughput sequencing (ATAC-seq) (53). Specific epigenetic modifications such as chromatin accessibility via histone acetylation/methylation play essential roles in response to viral infection (77–79). Shared epigenomic patterns of aging result in decreases in naïve T cells and increases in monocytes and cytotoxic cell functions. However, the magnitude of alterations is more significant in men than in women, with an accompanied loci-specific methylation decline in the B cells (53). As such, sex and age differences in epigenetic patterns of immune cells, in part, can explain variability in the severity of COVID-19.

Moreover, the epigenetic changes in CpG-sites located in subtelomeric regions that control innate immunity can mediate inflammatory responses to COVID-19. Chronic viral infection can accelerate aging as measured by the "epigenetic clock" (80). It remains to be elucidated whether

these epigenetic clocks based on chronological or biological age (80, 81) can predict the severity

of COVID-19 and subsequent exacerbation of chronic diseases in COVID-19 survivors.

Telomere attrition

Telomeres, which are repetitive nucleotides (TTAGGG)n at the ends of each chromosome, play

a role in maintaining genome stability and regulate innate immunity in response to viral

infection. Regions near telomeres called subtelomeres contain CG-enriched genes that regulate

innate immunity (82). Influenced by telomere length, these genes regulate telomere repeat-

containing RNA (TERRA) transcription, and their expression can be upregulated in response to

viral infection via activation of interferon-stimulated genes (ISGs). Therefore, diverse telomere

lengths often observed with aging immune cells (83) can underlie differential responses to viral

challenge (82). Another consequence of telomere attrition is the premature induction of genome

instability in viral-specific CD8^{+} memory T cells that results in senescent or antiapoptotic cells

(84). Thus, telomere attrition, coupled with dysregulated innate and adaptive immune responses

to viral infection, is another hallmark of aging that can contribute to the severe outcomes in older

adults with COVID-19.

Impaired Autophagy

The process of autophagy is modified by aging and thus can play a role in controlling viral

infection through diminished viral degradation, as well as by dysregulating innate and adaptive

immunity (85).

The autophagy process includes the functions of several protein complexes. In the absence of

stress, the mTORC1/ULK1/2 complex inhibits the initiation of autophagy. Under stress,

including viral infections, mTORC1 is inhibited, which subsequently activates a series of

proteins that results in the induction of autophagy and virion encapsulation and degradation of viral particles (86).

Moreover, autophagy regulates the bridge between the innate and adaptive immune responses to viral infection by inducing APCs such as B cells, macrophages, and dendritic cells. APCs, in turn, present viral antigens to CD4$^+$ T cells to release cytokines and regulate adaptive immune responses. The early autophagic process induces the release of interferon-gamma (IFN-γ) from CD4$^+$ T cells to promote CD8$^+$ T cells, NK cells, and macrophages in response to viral infection (87). Moreover, the autophagic process controls the inflammatory response, preventing the accumulation of ROS and the inflammasome pathway via targeting pro-IL-1β for lysosomal degradation (88). While some viruses evade the direct autophagy-mediated function, immune-mediated effects of autophagy can still control viral infection and inflammatory-mediated tissue damage. Therefore, impaired autophagy, a hallmark of aging, possibly contribute to the severity of COVID-19 and poor outcomes in older patients. Niclosamide and valinomycin, two FDA-approved drugs for other purposes, enhance autophagy and diminish viral replication (89). However, the antiviral effect of polyamines, such as spermidine, a bolster of autophagy, has been debated (90). Of note, rapamycin and its analogs, and also Vitamin D3, drugs with suggestive anti-aging effects, have antiviral efficacy by increasing autophagy (91). Despite its immunosuppressive effects in transplant patients, rapamycin inhibition of mTORC1 improves immune function in older adults and increases the response to vaccines; some clinical trials using rapamycin have shown no serious side effects in humans (92–95). Therefore, rapamycin, by improving immunity, is expected to improve outcomes in older adults with COVID-19.

Interventions to mitigate COVID-19 in aging

Clinical manifestations of COVID-19 have indicated that host–virus interactions such as cytokine storm and coagulopathy, underlying comorbidities, and possibly polypharmacy are all possible culprits for the spectrum of COVID-19 severity. To combat both acute and chronic conditions related to COVID-19, enhancing response to the vaccine and antiviral therapies using drugs that boost immune system response and enhance body system health is warranted. Older adults with an attenuated response to vaccine or antiviral medications might skew the pandemic figure toward epidemy in the older population. Therefore, some anti-aging modalities possibly attenuate the severity of COVID-19 and increase response to vaccines when they become available. Thus, combating SARS-CoV-2 require methods that go beyond direct targeting of the virus to include those approaches that support bodily system function via improving immunity, especially in older adults.

As such, interfering with pathways associated with the hallmarks of aging has the potential to improve the response to antiviral drugs (96). Potential drugs include agents that reduce mitochondrial ROS production and boost the immune system. Rapamycin has been shown to increase the immune response to the influenza vaccine and boost immune function in older adults (93, 94). Metformin, an old antidiabetic drug and also a candidate anti-aging modality, interferes with viral replication and host–viral interactions (97). Increasing Sirt6, an enzyme regulating multiple age-related signaling pathways, has been shown to reduce the immense inflammatory response to the fatal dengue virus infection (98). Some of the chloroquine-related family drugs, which are treatment candidates for prevention and treatment of COVID-19, also interfere with beta-galactosidase, a marker of senescence in cells (99). However, the efficacy and safety of chloroquine drugs in older adults require more data.

Although lists of drugs and vitamins have been suggested, approved anti-COVID-19 drugs remain to be recognized (100). More importantly, at this writing, none of the ongoing clinical trials has considered recruiting older patients. Thus, the impact of all potential therapies and safety in older adults remains to be determined. We suggest an accelerated understanding of the interactions between COVID-19 and the host hallmarks of aging in order to identify biomarkers with which to screen individuals at higher risk. Understanding the mechanisms of COVID-19 will likely arise from comparing the disease risks and response to treatments in young men and women with COVID-19 versus older patients—to do this, we need to include older adults in clinical trials.

Conclusion

The COVID-19 outbreak is a worldwide public health problem with health consequences that are likely to persist for many years. Currently, older adults and patients with comorbidities and other unknown risk factors have developed more severe and critical complications, and therefore are at a higher mortality risk. Both the incidence and severity of disease appear to be more prominent in men than women, which can be partially explained by both age-dependent and independent sex-dimorphism in the immune system. Coronaviruses use host factors for replication; these factors are impacted by age and the same mechanisms as those linked with the hallmarks of aging. Some of the hallmarks of aging, coupled with immune system responses and comorbidities, seem likely to play a pivotal role in the severity of COVID-19. Innate immunity with cytokine storms, coagulopathy, neutralizing antibodies; cellular immune responses such as $CD4^+$ and $CD8^+$ T cells, B cells, natural killer cells, monocyte and macrophages, and inflammatory host responses; along with specific virus antigen epitopes—all have interactive roles in disease development. Diminished reserves and stress response capacity, coupled with

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reduced immune response to vaccines place older adults at higher risk for critical health complications and mortality, especially during times of acute stress. Together with antiviral interventions, the key hallmarks of aging can offer insights for the identification and treatment of patients most at risk and help elucidate the basis for age and sex differences in response to such stressors. Application of candidate anti-aging drugs such as rapamycin and metformin, and antiviral drugs with potential senolytic effects possibly boost the immune system of older adults. Further investigation requires immediate attention. Such drugs can also prevent the possible post-COVID-19 accumulation of morbidities and accelerated biology of aging.

Conflict of interest

None.

Acknowledgments

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Table 1. COVID-19 structural, nonstructural, and accessory proteins

Replication phase	Host factor	Virus factor	Function
Binding and entry	ACE2	Spike glycol protein (S)	Cellular receptor
Attachment and entry		S glycoprotein	
Viral transcription/replication, ribosome frameshift		Replicase polyprotein 1a (R1a)	
Viral transcription/replication, ribosome frameshift		replicase polyprotein 1ab (R1ab)	
Protein 3a		Independent budding	Induction of apoptosis
3b			Inhibition of type I interferons, induction of apoptosis
Envelope small membrane protein (E)		Independent budding	
Membrane protein (M)		Virion morphogenesis	
Nonstructural protein 6 (NS6)			Inhibition of type I interferons, alteration in cellular DNA synthesis

Nonstructural protein (9) 7a (Ns7a)			Activate inflammation (MAPK-8) and NF-κB pathways
Protein 7b (Ns7B)			Unknown
Ns8a Ns8			Induction of apoptosis alteration in cellular DNA synthesis
Nucleoprotein (N)		Viral genome packaging	
Ns14		Exonuclease and repair activity	
Ns 9b			Unknown
Ns10			Unknown
	IFITM (interferon-induced transmembrane)		Inhibit cell entry
	TMPRSS2 (Transmembrane protease serine2)		Cleave and activate S protein
	Furin		Cleave and activate S protein
Genome replication and	GSK3		Phosphorylate N protein

transcription	Glycogen synthase kinase 3		and facilitate viral replication
Translation of structural proteins	N-linked glycosylation enzymes in Golgi		Modify S and M protein; N-linked glycosylation of the S protein facilitates lectin-mediated virion attachment and constitutes some neutralizing epitopes
	Endoplasmic reticulum chaperones		Proper folding and maturation of protein

Figure 1. The schematic figure implies the interaction between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with the cell structures, clockwise including cell membrane, endoplasmic reticulum, Golgi, extracellular matrix, followed by hallmarks of aging such as senescence cells, inflammation, genome instability, mitochondrial function, telomere length, epigenetics, and stem cell exhaustion. The entire cell fitness is required to combat viral infection, and coronavirus engages cell systems.

 Figure 2a. COVID-19 proteins.

Figure 2b. Coronavirus structure, cell entry, and replication.

ACE2: Angiotensin-converting enzyme2, ERGIC: Endoplasmic reticulum-Golgi intermediate compartment, ER: endoplasmic reticulum.

Figure 3. Mitochondria, outer membrane permeability and apoptosis pathways.

Apoptosis induced by coronavirus infection including intrinsic and extrinsic apoptosis.

Ligands: FasL, Fas ligand**,** TNF-α, tumor necrosis factor alpha**, antiapoptotic factors:** Bcl2-associated X; Bcl-xL, Bcl-2-like protein 1; Bcl2, B cell lymphoma 2, Mcl1, myeloid cell leukemia 1; **proapoptotic factors:** PUMA, p53-upregulated modulator of apoptosis; BAD, Bcl2-associated agonist of cell death; BAX; BID, BH3-interacting domain death agonist; BIM, Bcl2-interacting mediator of cell death; APAF1, apoptotic peptidase-activating factor 1; Casp: caspase; FADD: Fas associated via death domain; AKT: RAC-alpha serine/threonine protein kinase; SARS, severe acute respiratory syndrome (70).