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REVIEW ARTICLE

Role of senescence in the chronic health consequences of COVID-19

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While the full impact of COVID-19 is not yet clear, early studies have indicated that upwards of 10% of patients experience COVID-19 symptoms longer than 3 weeks, known as Long-Hauler's Syndrome or PACS (postacute sequelae of SARS-CoV-2 infection). There is little known about risk factors or predictors of susceptibility for Long-Hauler's Syndrome, but older adults are at greater risk for severe outcomes and mortality from COVID-19. The pillars of aging (including cellular senescence, telomere dysfunction, impaired proteostasis, mitochondrial dysfunction, deregulated nutrient sensing, genomic instability, progenitor cell exhaustion, altered intercellular communication, and epigenetic alterations) that contribute to age-related dysfunction and chronic diseases (the "Geroscience Hypothesis") may interfere with defenses against viral infection and consequences of these infections. Heightening of the low-grade inflammation that is associated with aging may generate an exaggerated response to an acute COVID-19 infection. Innate immune system dysfunction that leads to decreased senescent cell removal and/or increased senescent cell formation could contribute to accumulation of senescent cells with both aging and viral infections. These processes may contribute to increased risk for long-term COVID-19 sequelae in older or chronically ill patients. Hence, senolytics and other geroscience interventions that may prolong healthspan and alleviate chronic diseases and multimorbidity linked to fundamental aging processes might be an option for delaying, preventing, or alleviating Long-Hauler's Syndrome. (Translational Research 2022; 241:96–108)

Abbreviations: AMPK = AMP-activated protein kinase; COVID-19 = coronavirus disease 2019; COVID-FIS = A phase 2 placebo-controlled pilot study in COVID-19 of Fisetin to Alleviate Dysfunction and Excessive Inflammatory Response in Older Adults in Nursing Homes; CR = caloric

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restriction; FGA = Facility for Geroscience Analysis; ICU = intensive care unit; IF = intermittent fasting; LTCF = long-term care facility; MCC = multiple chronic conditions; MERS-CoV = Middle East Respiratory Syndrome Coronavirus; mTOR = mammalian target of rapamycin; NAD^+ = nicotinamide adenine dinucleotide; NMN = nicotinamide mononucleotide; NR = nicotinamide riboside; PACS = postacute sequalae of SARS-CoV-2 infection; PAMPs = pathogen-associated molecular profile factors; ROS = reactive oxygen species; SARS = severe acute respiratory syndrome; SARS-CoV-1 = severe acute respiratory syndrome coronavirus 1; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SASP = senescence-associated secretory phenotype; SNF = skilled nursing facility; TGN = translational geroscience network; WHO = World Health Organization

INTRODUCTION

Incidence/prevalence of Long-Hauler Syndrome. Initial reports from the World Health Organization (WHO)-China in February, 2020 indicated that clinical recovery from time of onset of COVID-19 symptoms is between 2-6 weeks, the latter being in more severe cases.[1] As the pandemic progressed, patients reported experiences of prolonged recovery times and lingering symptoms. This condition has received many names: PACS, Post-COVID, Long-COVID, Long-Haul COVID, or Long-Haulers Syndrome[2-4] Though loosely defined, "Long-Haulers" denotes patients who experience persistent symptoms after having acute COVID-19. The long-term sequelae of the virus are largely unknown, but initial reports of significant lung damage,[5,6] persistent myocardial inflammation,[7] kidney disease,[8] and neurological issues[9] are concerning, making the exploration of long-term impact at the mechanistic level urgent.

While the full impact of long-COVID is widely unknown, early reports suggested up to 10% of patients experience symptoms for over 3 weeks.[4] An early study from Italy showed that 87% of hospitalized patients reported at least one ongoing symptom 60 days after onset of the first COVID-19 symptoms, with 55% of patients reporting 3 or more ongoing symptoms.[10] In other cases, patients can experience a relapse in symptoms after an initial period of recovery.[11] These long-lasting symptoms can occur in adults across all age groups and may change and develop over time, regardless of severity of the acute case: asymptomatic patients can still develop Long-Hauler symptoms months later.[12,13] Data suggest that Long-Haulers impacts women at a higher rate, with one study finding women were 4 times more likely than men to be seen clinically for persistent symptoms.[11,13]

Globally, patients have expressed frustration with ongoing symptoms, lack of therapeutic solutions, and being directed to treatment for chronic fatigue syndrome and other nonspecific diagnoses. Little is known about why certain people are more susceptible to persistent symptoms after the acute case. However, innate immune system dysfunction and/or cellular senescence and accumulation of senescent cells, which contribute to age-related dysfunction and other chronic diseases, may provide insight into the increased risk of long-term sequelae in older patients. As the reported numbers of elderly or young chronically-diseased patients with Long- Haulers grow, more research is necessary about Long-Hauler Syndrome, its underlying mechanisms, the long-term impact of the virus, and potential interventions.

Working definitions of the syndrome. There have been many names given to symptoms lingering after the initial acute case of COVID-19, and there is overlap in this terminology. The UK National Institute for Health and Care Excellence (NICE) created the following clinical definitions of COVID-19 symptoms to help define cohorts of people experiencing prolonged symptoms: 1) acute COVID-19 is the initial onset of symptoms, with symptoms lasting up to 4 weeks; 2) ongoing symptomatic COVID-19 or Post-Acute COVID-19 includes symptoms lasting between 4 and 12 weeks; and 3) Post-COVID-19, Chronic COVID-19, Post-COVID Syndrome, or Long-Haulers Syndrome define symptoms lasting greater than 12 weeks not due to another condition.[4,14,15] The most inclusive definitions, "Long-COVID," or postacute sequalae of SARS-CoV-2 infection (PACS), involve symptoms lasting for any length of time over 4 weeks.[15,16]

COVID-19 IN THE ELDERLY AND PEOPLE WITH CHRONIC DISEASE

Adults over age 65 years and those with co-morbidities are at the greatest risk for mortality and morbidity from COVID-19.[17] Long-term symptoms of COVID-19, including fatigue, frailty, and weakness, are also changes that occur frequently in advanced old age in the absence of COVID-19 infection.

Disease burden and unique aspects of COVID-19 in older adults. As of September 2021, the β-coronavirus-19 (SARS-CoV-2) pandemic had led to 219 million confirmed cases and 4.5 million deaths worldwide. In the U.S., 81% of deaths were in individuals older than 65 years.[18,19] Mortality risk is increased in those living in a skilled nursing facility (SNF), partly due to the increased risk of transmission inherent to tightly-

confined congregate environments, particularly those in which a high proportion of residents are cognitively impaired and not able to comply with basic infection control practices. Additionally, systemic factors including underfunding, inadequate staffing, suboptimal infection control, and lack of personal protective equipment contribute to increased mortality risk in SNF.[20-22] Approximately 20% of SNF residents with SARS-CoV-2 die[23] and long-term care facility (LTCF) residents account for 32% of U.S. deaths, despite comprising only 5% of cases.[24]

COVID-19 presentation, prognosis, and long-term outcomes all have unique features in older adults. In LTCF, clinical presentations vary widely, with 31% of cases being asymptomatic and 37% of cases requiring hospitalization.[25] Presenting symptoms have some overlap with those in younger adults, including fever, cough, and hypoxia, which are relatively common.[26] However, more vague constitutional symptoms are among the most common in older adults, including fatigue, anorexia, and malaise.[25] Additionally, functional decline and delirium, without any focal signs or symptoms, are relatively common presentations.[27-29] Older adults in LTCF who are symptomatic tend to have long clinical courses, commonly lasting over 3 weeks.[25] Distinct clinical trajectories include survivors with few symptoms, symptomatic survivors, mortality following a prolonged clinical course, and mortality following a rapid clinical course, with each group having somewhat different patterns of initial signs/symptoms.[25] Those with higher symptom burden at the time of an initial positive test have poorer outcomes, though even older adults who are asymptomatic initially have greater mortality risk than those who test negative for COVID-19.[30] Age and comorbidities also have prognostic value, though multiple studies have shown that premorbid frailty is a good predictor of morbidity and mortality.[31-34] Premorbid cognitive impairment also increases mortality risk.[32] In addition to being an important predictor of outcomes from COVID-19 infection, frailty can also be a consequence, with accelerated frailty seen in older adults after infection.[35]

Predisposition to Long-Haulers chronic health consequences. Acute viral infections in general can lead to a number of long-term adverse outcomes.[36] For example, there is evidence of delayed neurologic sequelae following SARS-CoV-1 and MERS-CoV.[37,38] A study in 2009 examined the prevalence of chronic fatigue and long-term mental health problems after acute cases of SARS, and of the participants studied, over 40% had a psychiatric illness and 40% experienced chronic fatigue 31-50 months postinfection.[39]

Older adults with severe initial illness in intensive care units (ICU) can experience long-lasting symptoms, which is not unique to patients with COVID-19, called Post Intensive Care Syndrome (PICS). However, there is another group of patients with mild to moderate symptoms who did not need a lengthy hospitalization or intensive care stay, who present with similar features. Although a small uncontrolled study suggested that Long-Haulers patients can be young without having many pre-existing comorbidities, reports of older adults with Long-Haulers exist and comparative studies are needed to determine the impact of age on the incidence of the syndrome.[40] Many older patients have multiple pre-existing health conditions and these have been shown to be a factor that strongly predicts the persistence of symptoms.[12,40]

One specific example affecting older adults is Alzheimer's disease (AD). AD patients may have both decreased ability to recover to their preillness state after COVID-19 infection and have a direct effect of the virus on the brain condition, with 16% increases in death rates reported in 2020.[41,42] Older adults can have Multiple Chronic Conditions (MCC) and stratifying their risk for long term consequences should be quantified collectively, rather than by single-condition stratification.[43]

MECHANISMS

Geroscience hypothesis. The Geroscience Hypothesis proposes that targeting aging mechanisms, rather than targeting a single disease, can increase healthspan.[44-46] A corollary of this hypothesis is that aging mechanisms could be root cause contributors to the genesis of multiple diseases and disorders, even in younger people, as well as morbidity and mortality from diseases and other stresses (such as surgery, trauma, or infections). By understanding fundamental aging mechanisms and their relationship to the disease process of SARS-CoV-2, interventions that target fundamental aging processes, "geroscience interventions," may prove to be of value for treating Long-Haulers patients.

Pillars of aging. The "pillars of aging" include genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, dysregulated nutrient sensing, mitochondrial dysfunction, progenitor cell exhaustion, altered intercellular communication, and cellular senescence.[47,48] Each pillar can contribute to age-related disease and dysfunction, many are known to contribute to chronic diseases, and these aging mechanisms appear to be highly interrelated and even inter-dependent. Each pillar of aging may play a role in interfering with defenses against infection, including innate and adaptive immune responses,[49] and contribute to short- and long-term morbidity caused by infections.

Chronic viral infections, including HIV, can be associated with an accelerated aging-like state and early

onset of age-related diseases.[50] Such viral infections can lead to increases in oxidative stress, which can cause accumulation of DNA mutations and damage, leading to genomic instability, as well as mitochondrial dysfunction.[49,51,52] Telomere shortening and dysfunction, which naturally occurs as somatic cells replicate repeatedly, can lead to genomic instability.[53] The rate of attrition is dependent on a person's comorbidities, including age and disease.[53] Viruses and telomeres competitively utilize similar mechanisms for genomic maintenance.[54] The introduction of a viral infection can trigger a stress response, which can interfere with telomeric maintenance, causing telomere shortening.[54] One consequence of telomeric shortening or dysfunction, even in the absence of telomere shortening, is cellular senescence and impact on epigenetic age.[49,55-58]

Autophagy contributes to the maintenance of proteostasis by removing damaged, misfolded, or aggregated proteins, preventing proteotoxic stress, and facilitating immune responses to viral infections.[49,59] Mammalian Target of Rapamycin (mTOR), which regulates protein production, homeostasis, and autophagy, increases in activity with aging and can be increased in senescent cells.[49,60] Viral infections or other stressors can lead to increased mTOR activity, causing impaired autophagy and loss of proteostasis, accentuating severity of the infection.[49]

Decreased autophagy is linked to impaired regenerative function in progenitor cells.[61] Decreases in the regenerative capacity of progenitor cells, or progenitor cell exhaustion, can be caused by factors produced by senescent cells.[62-68] Viruses, including SARS-CoV-2, also impact progenitor cells, leading to detrimental long-term effects and increasing susceptibility to other age-related conditions.[69] Overall, the low-grade inflammation associated with aging increases the likelihood of developing more serious acute COVID-19 complications and risk of long-term symptoms.[70] The capacity of the immune system to clear infections decreases with age. Furthermore, immune system hyper-reactivity, leading to cytokine storm, is more likely to occur in the elderly.[70] However, patients who are considered immunocompromised and undergoing immune-suppressive therapy, including patients with HIV, may not benefit from targeting immune system hyper-reactivity.[71] Therapeutics for Long-COVID and more severe acute cases of COVID-19 need to be specifically studied in immunocompromised patients.

Cellular senescence and COVID-19. Hayflick and Moorehead first observed cellular senescence, an essentially irreversible cell fate, in human fibroblasts in 1961.[72] Cells that undergo senescence, senescent cells, are viable and resistant to apoptosis and can result from cellular replicative, metabolic, hypoxic, hyperoxic, or mechanical stresses, intracellular or tissue damage, cancerous mutations or oncogenes, radiation, chemotherapy and other drugs, activated immune cells such as neutrophils, or pathogens, among other signals.[73-81] Some, but not all, senescent cells can acquire a senescence-associated secretory phenotype (SASP). The SASP can entail release of cytokines, chemokines, proteases, reactive metabolites, growth factors, bioactive lipids, noncoding nucleotides (including microRNAs and cell-free mitochondrial DNA), and cellular particles (exosomes, microsomes).[82-84] These SASP factors can induce local and systemic inflammation, fibrosis, tissue damage, progenitor cell dysfunction, depletion of nicotinamide adenine dinucleotide (NAD^+) and increased production of reactive oxygen species (ROS) by nearby nonsenescent cells, induction of senescence in nonsenescent cells locally and systemically, blood clotting, impaired innate immune responses, and immune system dysfunction.[65,85-88] Thus, accumulation and sustained presence of senescent cells with a SASP can cause dysfunction and contribute to cognitive, metabolic, physical, and vascular dysfunction, tissue fibrosis, disease susceptibility and severity, and mortality.[44,68,85,89-98]

There can be benefits from cellular senescence, including facilitating removal of damaged tissues, protection against cancer, aiding in inflammatory responses, fetal development, and in the placenta to promote parturition.[74,99-101] Hence, interfering with the generation of senescent cells can lead to cancer, impair wound healing, and other consequences.[73,99,102] However, timely removal of those already formed senescent cells with a tissue-destructive SASP can alleviate dysfunction related to multiple diseases and aging in preclinical animal models, including delaying or reducing growth of cancers.[73,77,102] Our 'Threshold Theory of Senescent Cell Burden' holds that once senescent cells accumulate and spread to a threshold that is higher than that which the immune system can clear, further senescent cell accumulation and accelerated age- or disease-related dysfunction can ensue.[46,74,103]

Accumulation of senescent cells appears to confer risk for developing a more severe case or complications from COVID-19.[22,75,104] The SASP can impair immune system function.[87] Aging of the immune system, or immunosenescence, involves an increase in baseline levels of cytokines, including IL-6, IL-RA, TNF-α, and IL-1, which are also SASP factors.[105] There are increases in pro-inflammatory cytokines in patients with COVID-19, and these levels are related to the severity of cases and clinical outcome.[106-110] An excessive inflammatory response to COVID-19 can lead to the worsening of infection and symptoms and, eventually, cytokine storm.[111]

It has been reported that complement-mediated microvascular injury is associated with the primary pathophysiology of both COVID-19 progression and long-COVID.[112,113] As complement activity differs with age and sex, these factors should be considered in future therapeutic and treatment studies.[114] Additionally, sustained complement activation may induce or accelerate senescent cell accumulation, which can lead to endothelial dysfunction, possibly contributing to long-COVID pathology.[113,115]

Amplifier/Rheostat hypothesis. Our team developed an 'Amplifier/Rheostat Hypothesis': that the pathogen-associated molecular profile factors (PAMPs) that are expressed by infectious agents can cause the SASP of pre-existing senescent cells to become even more inflammatory and destructive.[46,75] According to this Amplifier/Rheostat Hypothesis, the already increased inflammatory state of aged or chronically ill individuals who have increased pre-existing senescent cell burden, might become more pronounced with SARS-CoV-2 infection.[93,105] This hypothesis might explain why the elderly and patients with pre-existing, cellular senescence-associated conditions are more susceptible to either more severe cases of acute COVID-19 and/or prolonged effects after the initial acute infection, especially if new senescent cells are formed that exceed the senescent cell threshold.[75] Furthermore, coronaviruses, including SARS-CoV-2 virus, can cause previously nonsenescent cells to become senescent, in part through Toll-like receptor-3, and senescent cell abundance is higher in patients who die from COVID-19 from other causes.[93,116,117]

Unitary theory of fundamental aging processes. Though distinct in some respects, the hallmarks of aging may not be fully independent processes. Rather, it appears they are interconnected, with all playing a role in contributing to age-related diseases and disorders. The Unitary Theory of Fundamental Aging Processes posits that targeting one hallmark, or pillar, of aging may influence some or all of the others,[45,74] Therefore, intervention against one fundamental aging mechanism could impact many of the others. This suggests that intervening by targeting a single fundamental aging mechanism may lead to broad benefits because of an impact on others, potentially being of benefit for effectively alleviating age-related diseases and disorders, including acute infections and their consequences in elderly or chronically ill patients.

DIAGNOSIS

PASC/post-COVID/Long-Haulers/Long-COVID. The diagnosis of Long-Hauler Syndrome remains as elusive as agreement about a name for the condition. Currently there is no universal definition of the condition or any generally accepted diagnostic algorithm. Compounding matters, there are no specific, objective, consistent markers of pathology. Anecdotally, symptom patterns, combined with documented positive polymerase chain reaction tests for the SARS-COV-2 virus or antibody titers against COVID-19, have been used in practice.[40] However, despite an increasing number of patients obtaining care, the presentation of Long-Hauler Syndrome across diverse age groups, socioeconomic tiers, and ethnicities is not yet well documented, rendering diagnostic or prognostic reliance on these symptom constellations less than ideal.

Blood SASP factors are increased in Long-Hauler Syndrome. Factors including IL-6, IL-8, and IP-10, which are also SASP components, appear to predict the severity of acute COVID-19 infection.[118] Leukocytes can remain persistently infected by COVID-19, meaning inflammation can persist after the initial infection and acute symptom onset.[36,119,120] As indicated above, once above a threshold, senescent cells may persist or even continue to accumulate. Thus, persistence of senescent cells could contribute to innate immune dysfunction in Long-Haulers syndrome patients, and perhaps even contribute to persistence of virus, further compounding Long-Haulers syndrome. However, in one study, patients with mild Long-Haulers syndrome at least a month after acute COVID-19 infection did not have consistent increases in inflammatory mediators compared to controls who did not have fatigue and generalized pain after acute COVID-19.[121] In preliminary studies, we observed increases in markers of cellular senescence and certain SASP factors in patients with more severe Long-Hauler Syndrome that persisted for several months compared to controls (unpublished observations). More study is needed to determine if there are relations between senescence, innate immune dysfunction, and Long-Haulers syndrome. This is particularly important for understanding disease mechanisms in those with severe, persistent symptoms.

MANAGEMENT

Long-Haulers clinic—multilevel, patient-centered team-based care. Patients with Long-Hauler Syndrome present with a multitude of symptoms, the most prominent being profound fatigue, shortness of breath, subjective cognitive complaints, described as "brain fog," and neurological symptoms consistent with autonomic neuropathy.[40] This broad spectrum of ailments necessitates a multidisciplinary approach to care. One established program at a major academic medical center has successfully treated patients with Long-Hauler

Syndrome by coalescing experts from occupational medicine, neurology, physical medicine and rehabilitation, immunology, and specialists in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome.

Care can be divided into 5 distinct levels (Fig 1). The first focuses on assessment for complicating medical conditions, such as deep vein thrombosis and opportunistic infections. Once acute medical pathology has been ruled out, the next level of treatment guides patients through an individualized, paced activity program, often supervised by physical and occupational therapists. Medications may be used to control symptoms that interfere with activity and reconditioning, such as tachycardia, insomnia, and cough. The third level of treatment is psychosocial support. This is especially important as roughly 25% of patients have reported difficulties with anxiety and depression during Long-Hauler Syndrome, even without a pre-existing history of mental health conditions. The final 2 levels of treatment use specialist clinics for autonomic dysfunction and concussion to help with dysautonomia symptoms and subjective impaired cognition, respectively. In addition, patients can be educated about coping strategies that allow them to manage their condition best as they progress through the recovery process, which often takes 6-18 months.

Geroscience interventions. The quest for interventions to alleviate age-related dysfunction and diseases has recently intensified, with the focus aimed at prolonging healthspan and alleviating chronic diseases linked to fundamental aging processes, rather than life span at all costs. Currently, among the more promising geroscience interventions are senotherapeutics (senolytics and senomorphics, including metformin and rapalogs), NAD^+ precursors, other pharmaceuticals, exercise, and dietary interventions (Fig 2).

There are clinical trials underway testing the efficacy of pharmaceuticals that target the pillars of aging. Senolytics, agents that selectively eliminate senescent cells, have had promising effects in preclinical and early phase clinical trials. As discussed above, senescent cells accumulate in tissues with aging and at etiological sites of multiple chronic diseases and disorders, even in children. Senolytics help attenuate senescent cell burden to below the threshold needed for the immune system to effectively clear remaining senescent cells.

Also targeting senescent cells, senomorphics inhibit the SASP and so block harmful effects of those senescent cells with a SASP.[122] Among senomorphic compounds are Metformin and Rapamycin and its analogs.[123] Used primarily to treat diabetes, Metformin has been shown to impact several aging related mechanisms, including reducing ROS and DNA damage, decreasing senescent cell burden, and activating AMPK, so inhibiting effects of increased mTOR activity.[124-126] Metformin has been explored in preclinical models and is currently being tested in clinical trials as a possible intervention for age-related disorders.[127] There are indications of links between Metformin use and decreased severity of acute COVID-19 infection.[128-130]

Rapamycin and its analogs, rapalogs such as Everolimus or Sirolimus, inhibit mTOR.[131,132] Rapamycin inhibits hyperfunction of the immune system.[133]

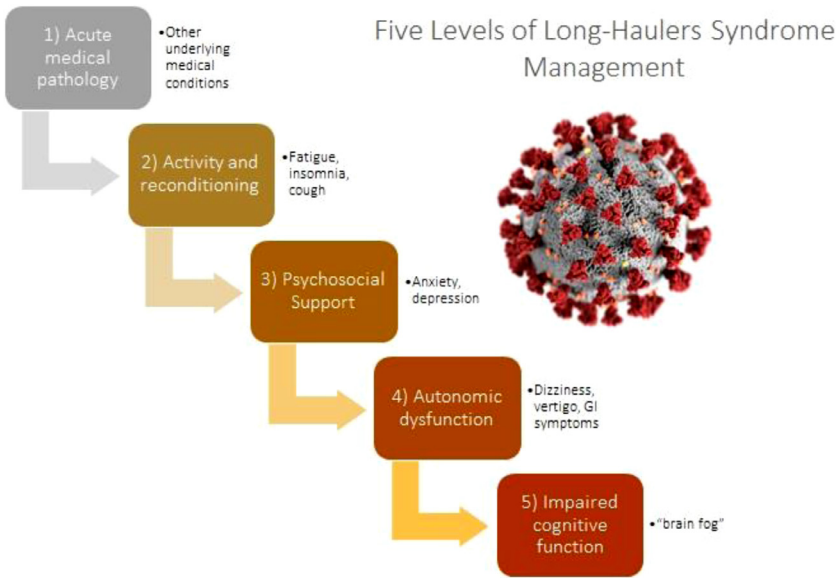

Fig 1. Care for Long-Haulers Syndrome patients is provided through a coordinated 5-level approach, each level designed to treat different subsets of symptoms.

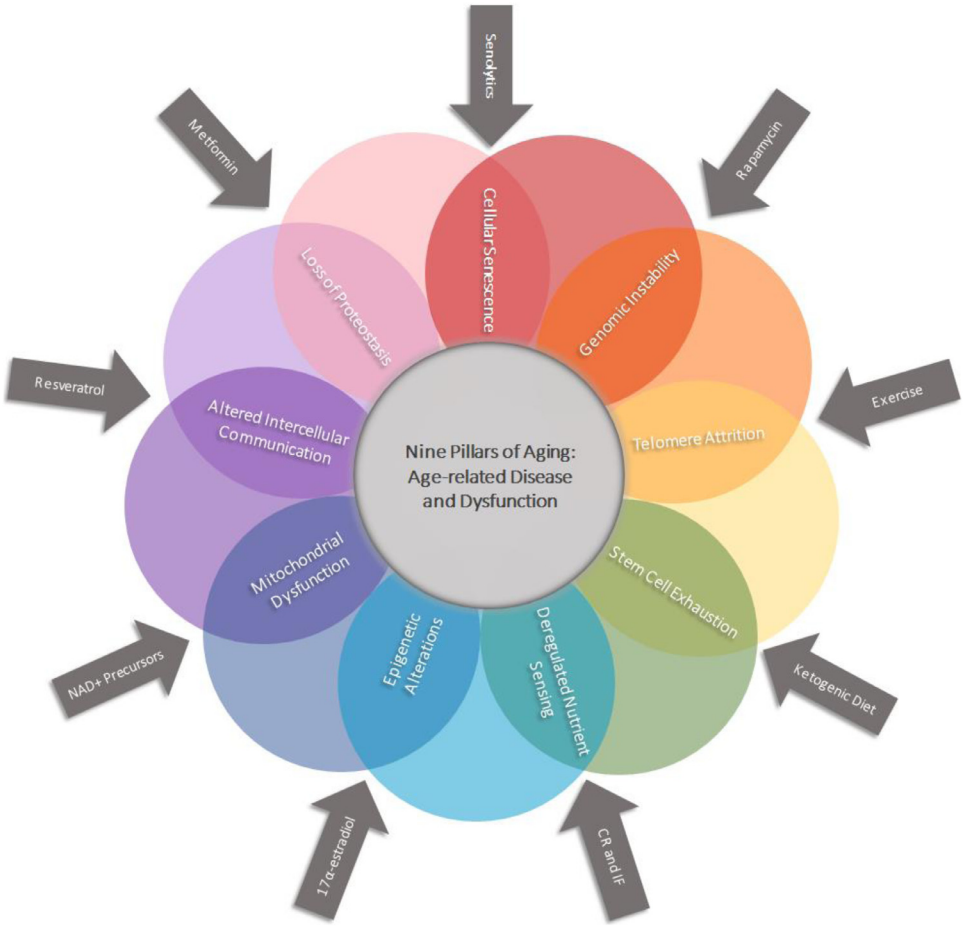

Fig 2. Based on Unitary Theory of Fundamental Aging Mechanisms, all 9 pillars of aging are interdependent and impact one another. Intervening with Geroscience Interventions against any one aging process may have an impact on several, if not all the other aging mechanisms, suggesting a role for multiple treatment targets for age-related diseases.

Rapamycin has been approved to treat lymphangioleiomyomatosis, an invasive lung disease[134] and has been shown to extend healthspan and lifespan in mice.[133,135] Some have suggested that long-term preventative usage of Rapamycin might decrease COVID-19 vulnerability and mortality in the elderly.[133] Furthermore, as an mTOR inhibitor, Rapamycin might temper the overall immune response to viral infections and decrease cytokine storm.[133,136,137]

Senescent cells promote accumulation of the leukocyte ectoenzyme, CD38, which degrades NAD^+ and is associated with the age-related decline in NAD^+.[88,138] Decreased NAD^+, in turn, can lead to generation of ROS and metabolic dysfunction.[139,140] Removal of senescent cells by senolytics leads to reduced CD38 activity, and as a result, partially prevents NAD^+ depletion.[88] Besides senolytics including flavonoids, other pharmacological interventions targeting the age-related increase in CD38 activity include anti-CD-38 antibodies and CD38 inhibitors.[141] Another option to counter the decline of NAD^+ with aging is NAD replacement therapy with NAD^+ precursors, including nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN).[138,142]

Resveratrol, a sirtuin agonist and polyphenol, has antioxidant properties and is found in common foods including grapes, red wine, and peanuts.[143] It appears to have antiviral properties both *in vivo* and *in vitro,* including inhibiting replication of the COVID-19-like MERS-CoV virus.[143-145] Thus, resveratrol might be a possible therapeutic option against SARS-CoV-2.[145]

17α-estradiol, in contrast to 17β-estradiol, is an essentially nonfeminizing estrogen that is present in both male and female mammals.[146,147] It declines with aging. 17α-estradiol treatment might alleviate some neurodegenerative disorders and has been shown to extend lifespan in mice and reduce metabolic dysfunction.[148-150] This steroid might be an intervention option for long-term impacts of COVID.

Ketogenic diets and ketogenic agents reduce fat mass and obesity, one of the major risk factors for

COVID-19 complications.[151,152] Ketogenic diets and agents could also help modulate the cytokine storm by decreasing ROS through an increase in mitochondrial metabolism. Ketogenic diets have shown promise in mouse models as a potential treatment against morbidity from viral infections.[153-155]

Other dietary modifications, such as caloric restriction (CR) and intermittent fasting (IF), have also been shown to be effective therapies against age-related disease and dysfunction.[156-158] IF consists of an alternating feeding schedule, whereas CR limits daily caloric intake without malnutrition. CR and IF reduce oxidative stress and inflammation.[158,159] IF and CR mimic Rapamycin by inhibiting the mTOR pathway and promoting autophagy.[160,161] Future work is needed to explore IF, CR, and autophagy inducers, as these interventions might help protect against COVID-19.[160,161]

Exercise can help reduce risk factors in older adults for COVID-19, including frailty and chronic disease.[162,163] Furthermore, exercise has immunoregulatory effects on both the innate and adaptive immune systems, which help in fighting against viral infections.[162] Regular exercise has been linked to release of anti-inflammatory cytokines and inhibition of pro-inflammatory cytokines.[164-166] Multimodal exercise might be a therapy to help prevent and fight acute COVID-19 infection.[167] Exercise and physical therapy are commonly prescribed for patients suffering from Long-COVID.[168]

Trials of senolytics. Multiple clinical trials are currently underway to investigate a potential role for senolytics in COVID-19 infection in older adults. COVID-FIS (A Phase 2 Placebo-Controlled Pilot Study in COVID-19 of Fisetin to Alleviate Dysfunction and Excessive Inflammatory Response in Older Adults in Nursing Homes; NIH R01AG72301; FDA IND149813; ClinicalTrials.gov Identifier: NCT04537299) includes SNF residents aged > 65 years who have tested positive for COVID-19 by rtPCR and have oxygen saturation >85% on 2 liters/minute or less of supplemental oxygen. Exclusion criteria are designed to preserve eligibility for most SNF residents, even those with several chronic diseases and polypharmacy, and do not exclude potential participants due to use of other agents to treat COVID-19 infection, either previously to or concurrently with Fisetin. Participants are randomized 1:1 to receive either Fisetin (~20 mg/kg/day) or placebo either orally or by NG or D tube twice for 2 consecutive days (days 0, 1, 8, and 9). They are followed for 6 months. Facilitating administration to older adults, including those with swallowing dysfunction, both Fisetin and the placebo have no odor or taste, and can be mixed with food or beverages. The primary outcome of the COVID-FIS study is incidence of progression on a 7-point ordinal severity scale adapted from the WHO Ordinal Scale for clinical improvement of SARS-CoV-2. Secondary outcomes include measures of senescent cell abundance/inflammation, physical dysfunction/frailty, safety/tolerability, various laboratory parameters, chest imaging, need for acute hospital transfer, ICU care, intubation, mortality, and development of Long-Hauler syndrome.

COVID-FISETIN (A Phase 2 Placebo-Controlled Pilot Study in COVID-19 of Fisetin to Alleviate Dysfunction and Excessive Inflammatory Response in Hospitalized Adults; NIH R01AG72301; FDA IND149813; ClinicalTrials.gov Identifier: NCT04476953) is an analogous trial targeting adults who are hospitalized with COVID-19 infection. Eligible individuals are those aged ≥ 60 years (or age ≥ 18-59 years with at least one comorbidity that is associated with increased COVID-19 disease severity) who are hospitalized with COVID-19 infection and have $SpO_2 \geq 85\%$ on room air or ≤ 2 L of supplemental oxygen. Participants are randomized 1:1 to receive either Fisetin (~20 mg/kg/day) or placebo either orally or by NG or D tube for 2 consecutive days at study outset and are subsequently followed for 6 months. The primary outcome is oxygenation status as measured by S/F ratio: SpO_2/FiO_2. Secondary outcomes include prevention of deterioration in physical function (frailty), progression from mild/moderate to severe/critical infection, safety and tolerability of Fisetin, and development of Long-Hauler syndrome.

Combining therapies. Building on the Geroscience Hypothesis and importance of intervening at a mechanistic level, our Unitary Theory of Fundamental Aging Mechanisms posits that interventions against one aging mechanism might impact other processes. Combining geroscience interventions to fight COVID-19 as a multimechanistic approach might improve outcomes for older adults.

CONCLUSIONS AND FUTURE DIRECTIONS

Research needed—specific areas requiring future investigation. While senescence and other pillars of aging provide reasonable insight into the possible processes involved and risks for Long-Hauler Syndrome, detailed mechanisms of the SARS-CoV-2 and its impact on older adults need to be further explored. Furthermore, therapeutics specifically targeting those mechanism need to be tested in clinical trials.

The Translational Geroscience Network (TGN) was established to accelerate Geroscience research. Multiple institutions that constitute the TGN (Mayo Clinic, Harvard, John Hopkins, Wake Forrest, St. Jude's, Steadman Clinic, and the Universities of Minnesota, Michigan, and Connecticut, and the University of

Texas Health Sciences Center at San Antonio) run clinical trials in parallel. The TGN's Facility for Geroscience Analysis (FGA), located at Mayo Clinic, develops innovative assays and laboratory tests for aging markers and ways to test for efficacy of therapeutics. Hopefully, despite considerable barriers to clinical trials, the TGN model will help streamline clinical research and the development of therapeutics for a growing aging population, including SNF residents.

As the number of people impacted globally by COVID-19 grows each day and the SARS-CoV-2 evolves into new variants, it is imperative for research efforts to keep up. Though knowledge about long-term outcomes of COVID-19 is still limited, we know enough to understand the importance of finding treatment options for patients suffering from Long-Hauler Syndrome. Senolytics that show early promise as an effective treatment for other senescence related diseases and disorders are currently being explored in this population.

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