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.

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COVID-19, ferrosenescence and neurodegeneration, a mini-review

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A B S T R A C T

Exacerbation of cognitive, motor and nonmotor symptoms have been described in critically ill COVID-19 patients, indicating that, like prior pandemics, neurodegenerative sequelae may mark the aftermath of this viral infection. Moreover, SARS-CoV-2, the causative agent of COVID-19 disease, was associated with hyperferritinemia and unfavorable prognosis in older individuals, suggesting virus-induced ferrosenescence.

We have previously defined ferrosenescence as an iron-associated disruption of both the human genome and its repair mechanisms, leading to premature cellular senescence and neurodegeneration. As viruses replicate more efficiently in iron-rich senescent cells, they may have developed the ability to induce this phenotype in host tissues, predisposing to both immune dysfunction and neurodegenerative disorders.

In this mini-review, we summarize what is known about the SARS-CoV-2-induced cellular senescence and iron dysmetabolism. We also take a closer look at immunotherapy with natural killer cells, angiotensin II receptor blockers ("sartans"), iron chelators and dipeptidyl peptidase 4 inhibitors ("gliptins") as adjunct treatments for both COVID-19 and its neurodegenerative complications.

1. Introduction

COVID-19 disease is caused by the SARS-CoV-2 virus that, after originating in the city of Wuhan, China, spread rapidly throughout the world. Initially, it was believed that this infection affected only the respiratory tract, but the emergence of gastro-intestinal (GI), neurologic and hematologic symptoms attested to its more systemic nature (Pryce-Roberts et al., 2020). The central nervous system (CNS) involvement, found in nearly 40% of critically ill COVID-19 patients, is heralded by strokes, cognitive dysfunction, depression, psychosis and delirium, suggesting that this virus may predispose to neurodegenerative disorders (Banerjee and Viswanath, 2020).

Although Alzheimer's (AD) or Parkinson's disease (PD) have not been described in association with COVID-19, exacerbation of preexisting cognitive, motor and non-motor symptoms was often observed, indicating viral neurotropism (Banerjee and Viswanath, 2020; Brown et al., 2020; Heneka et al., 2020; Mao et al., 2020; Rogers et al., 2020; Jin et al., 2020). In addition, several prior pandemics have been accompanied by neuropsychiatric sequelae, suggesting that these outcomes could be expected in the aftermath of COVID-19 (Troyer et al., 2020; Tipton and Wszolek, 2020).

The association of unfavorable COVID-19 prognosis with advanced chronological age, hyperferritinemia and lymphopenia suggests that SARS-CoV-2 may disrupt host antiviral immunity by inducing iron dyshomeostasis (Malavolta et al., 2020; Sargiacomo et al., 2020). As SARS-CoV-2, like other viruses, may be iron-dependent, it likely promotes ferrosenescence to acquire this metal and disable host natural killer cells (NKCs) (Drakesmith and Prentice, 2008; Schmidt, 2020a; Cavezzi et al., 2020; Nuñez and Chana-Cuevas, 2018; Colafrancesco et al., 2020).

In a previous article, we defined ferrosenescence as iron-induced disruption of both DNA and its p53-mediated repair, resulting in premature cellular senescence and neurodegeneration (Sfera et al., 2018). As p53 drives the NKC elimination of senescent and virus-infected cells, SARS-CoV-2 may exploit this protein to optimize thriving. Indeed, decreased p53 and NKCs count were documented in severely ill COVID-19 patients, suggesting virus-usurped immunity (Singh and Bharara, 2020a; Market et al., 2020).

In this mini-review, we examine the SARS-CoV-2 hijacking of NKCs and its link to neurodegeneration via iron-induced genomic and mitochondrial damage. We also take a closer look at NKCs immunotherapy, angiotensin II receptor blockers ("sartans"), iron chelators and dipeptidyl peptidase 4 inhibitors ("gliptins") as adjunct therapies for COVID-19 and neurodegeneration.

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2. SARS-CoV-2 entry portals and iron dyshomeostasis

New research has shown that SARS-CoV-2 accesses host tissues by usurping several cell membrane and mitochondrial receptors associated with cellular senescence and iron metabolism. Viral exploitation of these proteins, including angiotensin converting enzyme 2 (ACE-2), dipeptidyl peptidase 4 (DPP4), furin and cluster of differentiation 147 (CD 147), disrupts the function of NKCs, facilitating the development of both COVID-19 critical illness and neurodegeneration (Schmidt, 2020a; Cavezzi et al., 2020; Nuñez and Chana-Cuevas, 2018; Colafrancesco et al., 2020) (Radzikowska et al., 2020; Xie et al., 2011). Indeed, as viruses replicate more efficiently in senescent cells, they likely hijack the mechanisms controlling their elimination (Earls et al., 2020; Jadidi-Niaragh et al., 2012; Araga et al., 1991; Mihara et al., 2008).

In the following, we focus on the SARS-CoV-2 entry portals and their association with ferrosenescence-induced NKCs dysfunction.

3. ACE-2

The attachment of SARS-CoV-2 virus to ACE-2 protein is mediated by the host transmembrane serine protease 2 (TMPRSS2), an enzyme that primes the S antigen, activating the receptor binding site (RBS) (Hoffmann et al., 2020). SARS-CoV-2/ACE-2 binding likely impairs angiotensin II (ANG II) hydrolysis, leading to its unopposed accumulation (Sfera et al., 2020). Novel preclinical studies have linked ANG II to iron dyshomeostasis as this peptide regulates several iron proteins, including hepcidin, divalent metal transporter 1 (DMT1), ferroportin 1 (Fpn1) and transferrin receptor 1 (TfR1) (Chen et al., 2020; Ishizaka et al., 2007a). In addition, human studies have associated angiotensin receptor blockers (ARBs) with hemoglobin, further connecting ANG II with the release of iron (Mohanram et al., 2008; Cheungpasitporn et al., 2015). Moreover, hyperferritinemia and hemolytic anemia, recently associated with COVID-19 critical illness, also link the virus-upregulated ANG II to iron homeostasis (Pagani et al., 2019; Hindilerden et al., 2020; Lazarian et al., 2020).

Several novel studies have reported that ANG II triggers premature cellular senescence, an iron-abounding phenotype, likely facilitating the SARS-CoV-2 infection (Killilea et al., 2004). Indeed, several other viruses, including human immunodeficiency virus (HIV) and hepatitis B and C were demonstrated to induce cellular senescence by upregulating the host iron (Schmidt, 2020a) (Cohen and Torres, 2017; Idrissi et al., 2016; Naggie and Hepatitis, 2017). Conversely, ARBs were found protective against the senescence-mediated pathology, indicating their potential role in averting both COVID-19 complications and neurodegeneration (Prusty et al., 2017; Blagosklonny, 2017; Song and Kim, 2019; de Cavanagh et al., 2011).

Taken together, this data suggests that the SARS-CoV-2 virus acquires iron and disrupts NKCs by ferrosenescence. In return, this likely promotes neurodegeneration via the accumulation of senescent cells.

4. DPP4

The SARS-CoV-2 entry portal, DPP4, expressed on cell membranes and mitochondria, plays a major role in both type 2 diabetes mellitus (T2DM) and antiviral defenses (Sottile et al., 2019; Jiang et al., 2004; Koshiba et al., 2011; Lee et al., 2020). Like ACE-2, DPP4 has been linked to cellular senescence, suggesting that the SARS-CoV-2 virus thrives by promoting this phenotype. Indeed, previous studies have shown that DPP4 is an aging marker that prompts NKCs to eliminate the senescent cells expressing this protein (Kim et al., 2017). Viral attachment to DPP4 likely alters the receptor configuration, contributing to the accumulation of uncleared senescent cells (Klemann et al., 2016). In this regard, earlier studies have associated NKCs dysfunction with neurodegenerative disorders, including PD and AD (Earls et al., 2020) (Maghazachi, 2013a; Martínez-Cué and Rueda, 2020).

Aside from cellular senescence, DPP4 has been directly linked to ferroptosis, an iron-mediated nonapoptotic cell death, associated with both COVID-19 critical illness and neurodegeneration (Cavezzi et al., 2020) (Edeas et al., 2020a; Li et al., 2020). Under normal circumstances, ferroptosis is blocked by the p53 attachment to DPP4, suggesting that SARS-CoV-2 exploitation of this protein likely enables both viral infection and neurodegeneration (Xie et al., 2017; Zhang and Chen, 2019a; Liu et al., 2020a; Shen et al., 2014; Tarangelo and Dixon, 2018)(Fig. 1). Since p53 is instrumental for NKCs antiviral function, the virus may have developed a backup mechanism for the exploitation of this protein, utilizing two avenues, a direct disruption (via the S2 antigen) and an indirect one (via iron upregulation) (Xie et al., 2017) (Shen et al., 2014) (Fig. 2). On the other hand, DPP4 inhibitors (gliptins) are promising treatments for both COVID-19 and neurodegenerative disorders as they inhibit ferroptosis and restore the integrity of p53 (Angelopoulou and Piperi, 2018; Svenningsson et al., 2016; Solerte et al., 2020).

5. CD147

Another SARS-CoV-2 entry portal, CD147 or basigin, is expressed on both the host cell surface and mitochondria, an organelle essential for antiviral immunity (Ulrich and Pillat, 2020; Pablo and Ochrietor, 2013; Luo et al., 2014). In addition, CD147 regulates mitochondrial metabolic reprograming and the generation of lactate (Schneiderhan et al., 2009). Excessive lactate levels have been associated with NKCs dysfunction, linking CD147 to COVID-19 critical illness (Calvisi, 2016; Scott and Cleveland, 2016). Interestingly, CD147 and lactate dehydrogenase (LDH) are colocalized with the mitochondrial reticulum, suggesting that SARS-CoV-2/CD147 attachment could augment the release of LDH, a marker of COVID-19 mortality (Henry et al., 2020; Hashimoto et al., 2006). Moreover, CD147 is also the entry portal of *Plasmodium falciparum*, an iron-dependent pathogen associated with premature cellular senescence, further emphasizing the role of this phenotype in COVID-19 (Asghar et al., 2018; Frimpong et al., 2019; Clark et al., 2014; Huang et al., 2014). Interestingly, antimalarial drugs, chloroquine and hydroxychloroquine may block SARS-CoV-2/CD147 attachment, preventing iron-related pathology (Quiros Roldan et al., 2020).

Taken together, SARS-CoV-2/CD147 binding likely triggers ferrosenescence that, in turn damages the mitochondrion, disrupting NKCs-mediated antiviral immunity.

6. Furin

It was recently reported that SARS-CoV-2 exploits another host protein, furin that cleaves the S antigen into S2, a mediator of cell-to-cell fusion and a likely facilitator of viral migration from infected to noninfected cells (Hoffmann et al., 2020) (Xia et al., 2020). Interestingly, furin is a proprotein convertase with numerous physiological functions, including the conversion of pro-hepcidin to active hepcidin, further linking COVID-19 to iron metabolism (Wichaiyo et al., 2015). In addition, as mentioned above, the S2 antigen of SARS-CoV-2 may directly inhibit p53, sabotaging the elimination of virus-infected, senescent and possibly cancer cells (Singh and Bharara, 2020b; Zhang and Chen, 2019b; Ma-Lauer et al., 2016; Aloni-Grinstein et al., 2018; Jyotsana and King, 2020; Dai et al., 2020; Moujaess et al., 2020). Moreover, as p53 participates in both DNA damage repair (DDR) and senescent cells elimination, SARS-CoV-2 exploitation of this protein may predispose to neurodegeneration (Sargiacomo et al., 2020) (Funauchi et al., 2015; Collin et al., 2018; Kuo et al., 2020). Indeed, dysfunctional DDR and genomic damage have been associated with cellular senescence and neurodegenerative disorders (Madabhushi et al., 2014). Furthermore, inefficient DDR may lead to spillage of damaged DNA or mtDNA into the cytosol and the peripheral blood, probably accounting for this recently described COVID-19 marker (Liu, 2020).

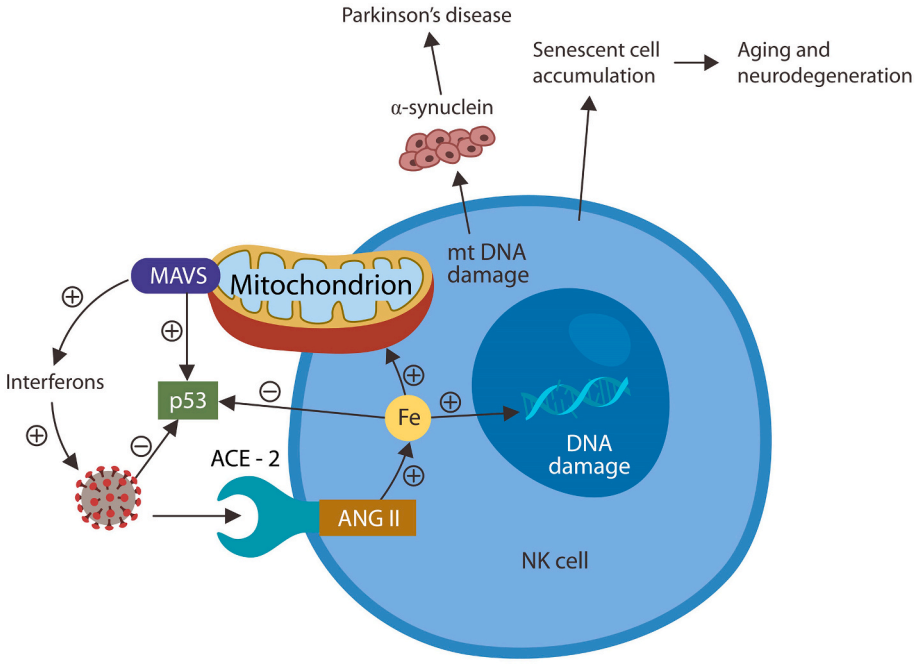

Fig. 1. A potential mechanism of NKCs hijacking by iron: SARS-CoV-2/ACE-2 attachment leads to ANG II accumulation. ANG II upregulates iron, inducing ferrosenescence that damages the DNA, mitochondrial DNA (mtDNA) and p53. ANG II can also inflict mitochondrial damage directly (not shown). Mitochondrial disruption promotes viral infection by impairing antiviral signaling (MAVS) and the release of interferon. SARS-CoV-2 antigen S2 can inhibit p53 directly, sabotaging viral elimination. Taken together, dysfunctional NKCs fail to eliminate senescent cells and α-synuclein, increasing the risk of neurodegeneration.

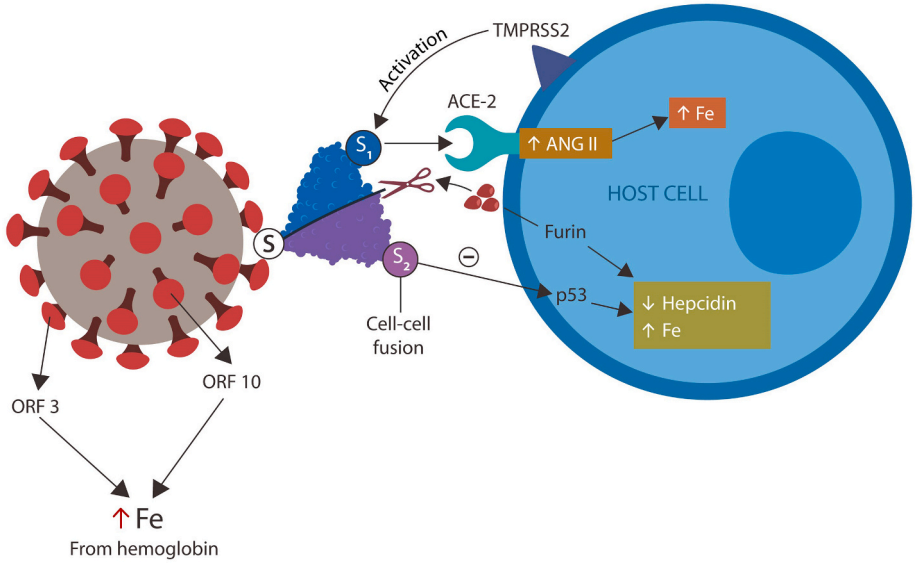

Fig. 2. The SARS-CoV-2-induced ferrosenescence: S antigen usurps host protease TMPRSS2 to prime this protein to S1, enabling ACE-2 attachment. Unopposed ANG II accumulation, augments intracellular iron, inducing DNA and mitochondrial DNA (mtDNA) damage. Furin cleaves, the S antigen into S2, a facilitator of cell-to-cell fusion and a p53 inhibitor. Furin also upregulates the iron protein hepcidin, increasing intracellular iron, further damaging the genome.

7. Viral accessory proteins

Several SARS-CoV-2 accessory viral proteins, including open reading frame (ORF) 3, 10 and possibly 8 were found to facilitate viral infection and iron dyshomeostasis via iron release from hemoglobin (Cavezzi et al., 2020) (Read, 2020). Indeed, novel studies have suggested that ORF proteins may cause the hemolytic anemia documented in severely ill COVID-19 patients (Lazarian et al., 2020) (Lippi and Mattiuzzi, 2020).

8. SARS-CoV-2 hijacking of NKCs

Several new studies have found a direct correlation between the COVID-19 prognosis and host hyperferritinemia or lymphopenia, suggesting that the virus likely exploits iron metabolism to disrupt NKCs antiviral function (Bolondi et al., 2020; Perricone et al., 2020; Edeas et al., 2020b; Vargas-Vargas and Cortés-Rojo, 2020; Gómez-Pastora et al., 2020). Others have reported that hyperferritinemia and premature cellular senescence predispose to both COVID-19 critical illness and neurodegenerative disorders, indicating a role for iron in both conditions (Sottile et al., 2019) (Masaldan et al., 2018; Kale et al., 2020). Conversely, iron deprivation has been shown to lower the viral load and improve prognosis in many viral infections (Liu et al., 2020b; Schmidt, 2020b).

NKCs are vigilant innate immune lymphocytes capable of locating and eliminating senescent, cancer and virus-infected cells without prior sensitization by the major histocompatibility complex (MHC) (Market et al., 2020) (Masselli et al., 2020). Inefficient senescent cells clearance

was demonstrated to dysregulate both neighboring cells and the circulating lymphocytes, increasing the chance of neurodegeneration (Pereira et al., 2019). Indeed, a recent PD preclinical study found that aside from senescent cells, NKCs also clear α-synuclein, connecting their impairment to neurodegeneration (Earls et al., 2020).

SARS-CoV-2 entry portals have been directly linked to the NKCs-driven elimination of senescent and virus-infected cells, suggesting that this virus triggers ferrosenescence to usurp host immunity (Jurewicz et al., 2007; Abadir et al., 2011). As some of these proteins are expressed on the mitochondrion and are crucial for NKCs antiviral immunity, their exploitation by the SARS-CoV-2, effectively hands control of these lymphocytes to the virus.

Under normal circumstances, the viral-host contact prompts the mitochondrion to release interferons via mitochondrial antiviral signaling (MAVS) protein (Kim et al., 2018). MAVS interaction with p53 activates the NKCs-driven elimination of senescent and virus-infected cells, therefore by exploiting this protein, SARS-CoV-2 hijacks the entire host antiviral defenses (Zhang et al., 2020; Mijit et al., 2020a). Indeed, viral infections and neurodegeneration have been directly corelated with mitochondrial damage (Maghazachi, 2013a) (van Erp et al., 2019; Cowan et al., 2019).

Taken together, SARS-CoV-2-induced ferrosenescence in NKCs, facilitates senescent cells accumulation and viral thriving, supporting the use of exogenous lymphocytes in the treatment of COVID-19 (NCT04365101) (NCT04344548) and neurodegenerative disorders (Earls et al., 2020) (Maghazachi, 2013a) (Song et al., 2020; Machhi et al., 2020).

9. Interventions

Several therapeutic modalities have been developed and are currently in clinical trials for COVID-19, including immunotherapy with NKC, ARBs, iron chelators and DPP4 inhibitors. Aside from protecting against SARS-CoV-2-related cognitive, motor and nonmotor symptoms, these interventions could address the symptoms of neurodegenerative disorders of other etiologies (Fig. 3).

10. NKCs immunotherapy

Live, exogenous NKCs derived from the peripheral blood or stem cell precursors are currently in clinical trials for COVID-19 as they likely enhance host antiviral defenses and senescent cells clearance (Market et al., 2020) (Hu et al., 2019) (NCT04344548). NKCs immunotherapy is easily administered as these lymphocytes do not require complex HLA matching and can be augmented by the addition of immune stimulatory molecules (Shimasaki et al., 2020).

This therapeutic modality has proved effective in amyotrophic lateral sclerosis and multiple sclerosis and is currently being assessed for other neurodegenerative disorders (Maghazachi, 2013b; Garofalo et al., 2020). Indeed, the NKCs immunotherapy could benefit patients with PD as, like influenza H5N1 and H1N1 viruses, SARS-CoV-2 may preferentially target the dopaminergic neurons in substantia nigra (Eldeeb et al., 2020). In addition, as NKCs accelerate the elimination of senescent cells and α-synuclein, they may comprise a "generic" treatment for multiple neurodegenerative disorders (Earls et al., 2020).

11. Sartans

Preclinical studies have shown that ANG II may interfere with iron absorption, suggesting that early interventions at this level could prevent the development of COVID-19 critical illness (Tajima et al., 2010).

The non-heme iron is absorbed in the duodenum via DMT1 transporter, a protein controlled by the SLC11A1 gene that also regulates NKCs activation (Su et al., 2020; Hedges et al., 2013; Czachorowski et al., 2009; Awomoyi, 2007). For this reason, SARS-CoV-2 exploitation of this gene likely induces iron dyshomeostasis and immune impairment. Conversely, preclinical studies have found that ARBs suppress DMT1 expression, suggesting a protective effect against SARS-CoV-2 at the gut level (Baral et al., 2020; Ishizaka et al., 2007b). In addition, ARBs were demonstrated to possess antiviral properties against other viruses, including dengue and HCV, suggesting that DMT1 inhibition may prevent viral usurpation of iron homeostasis (Baral et al., 2020; Ishizaka et al., 2007b; Eslami et al., 2014; Hernández-Fonseca et al., 2015; Colmenero et al., 2009; Mak et al., 2012; Saavedra, 2020). ARBs are currently in clinical trials against COVID-19 but their early or preventive use could block viral hijacking of SLC11A1 (NCT04335123) (NCT04312009)(NCT04311177). In addition, preclinical studies have found that ARBs may protect against PD, probably by DMT1 and ferrosenescence inhibition (Mertens et al., 2011; Villapol and Saavedra, 2015; Reardon et al., 2000; Lee et al., 2014; Perez-Lloret et al., 2017; Gebre et al., 2018). Furthermore, as ARBs were demonstrated to upregulate p53 and restore DDR, they may slower the development of cellular and immune senescence, lowering the risk of neurodegeneration (Mijit et al., 2020b; Gong et al., 2010; Blagosklonny, 2018).

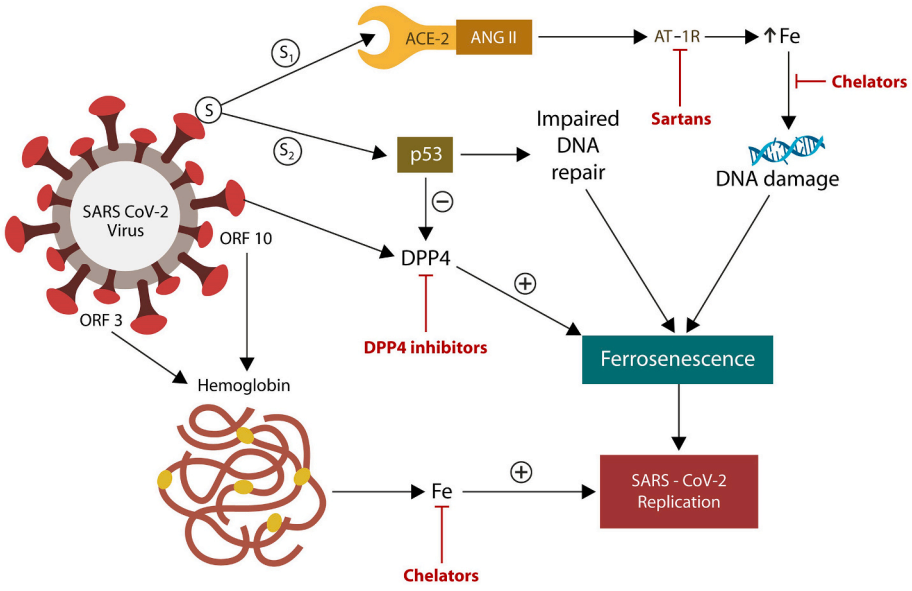

Fig. 3. The likely action mechanism of "sartans", "gliptins" and iron chelators is schematically illustrated along with viral ferrosenescence mechanisms. The SARS-CoV-2 virus upregulates intracellular iron (via angiotensin II accumulation), triggering DNA damage in host NKCs. In addition, the virus blocks p53, disrupting DNA damage repair (DDR). These two actions trigger ferrosenescence, facilitating viral replication. Viral accessory proteins attack hemoglobin, further increasing iron levels.

12. Iron chelators

Iron chelators, including deferoxamine, deferiprone and deferasirox possess antiviral actions against several viruses, including HIV, West Nile and HCV (Duchemin and Paradkar, 2017; Theurl et al., 2004; Georgiou et al., 2000; Williams and Meyer, 2009). As RNA viruses are more sensitive to iron chelators, they may be beneficial for COVID-19 and are currently in clinical trials for this condition (NCT04333550) (Dalamaga et al., 2020). Moreover, a recently developed, potent and natural iron chelator, DIBI, appears a likely SARS-CoV-2 treatment candidate, especially as it is well tolerated by older individuals (Thorburn et al., 2017; Kontoghiorghes and Kontoghiorghe, 2020). Several novel studies have reported that aside from denying iron to viruses, chelators also augment NKCs function, suggesting that they act both as antiviral and immune stimulatory agents (Sherman and Spear, 1993). Furthermore, iron chelators may upregulate p53, augmenting viral and senescent cells elimination, a role that has brought them into the field of neurodegenerative disorders (Zhang and Chen, 2019b; Ma-Lauer et al., 2016) (Muñoz-Fontela et al., 2011; Liang and Richardson, 2003). The SARS-CoV-2 antigen S2 appears to directly block p53, likely triggering ferroptosis, a cell death believed to be involved in both COVID-19 and neurodegeneration (Singh and Bharara, 2020a).

Taken together, iron chelators may inhibit SARS-CoV-2 by withholding iron from the virus, upregulating p53 and the NKCs antiviral function.

13. Gliptins

Gliptins, or DPP4 inhibitors are potential COVID-19 treatments currently in clinical trials as they are believed to reduce viral entry (Solerte et al., 2020) (NCT04365517). As gliptins may lower ferroptosis, a phenomenon that plays a major role in AD and PD, these agents may prove beneficial for neurodegenerative disorders (Mousa and Ayoub, 2019; Guiney et al., 2017; Yan and Zhang, 2020). In addition, since DPP4 marks senescent cells, their recognition and elimination by NKCs may avert accumulation (Kim et al., 2017).

Recently DPP4 has been associated with physical exhaustion and chronic fatigue syndrome (CFS), a major complaint of patients with viral infections, including COVID-19, suggesting that DPP4 inhibitors may ameliorate this pathology (Qi et al., 2020; Bühling et al., 1994; Fletcher et al., 2010; Wilson, 2020; Perrin et al., 2020; Silvestre et al., 2019). Several studies have associated CFS with ferroptosis and lipid peroxidation, indicating that iron may play a major role in the pathogenesis of CFS (Brkic et al., 2010; Swinkels et al., 2002). Indeed, cancer studies have connected ferroptosis to the p53-mediated DPP4 inhibition, suggesting that gliptins should be evaluated as CFS treatments (Xie et al., 2017) (Morris and Maes, 2012; Zhou et al., 2020).

Taken together, ferroptosis prevention with DPP4 inhibitors could preempt viral entry, fatigue and the development of neurodegeneration.

14. Conclusions

Like other viruses, SARS-CoV-2 may thrive in iron-rich senescent cells, a phenotype it likely promotes. Iron is a major senescence inducer as it disrupts both the DNA and its p53-mediated repair, triggering ferrosenescence. The SARS-CoV-2 virus may have developed the ability to evade host detection by triggering this phenotype in NKCs, disrupting their vigilance.

SARS-CoV-2 exploitation of iron metabolism likely begins at the level of GI absorption by the diversion of SLC11A1 gene, a regulator of both ferroptosis and NKCs activation. Iron metabolism is further usurped at viral entry portals, enabling infection and contributing to neurodegeneration. Because of these reasons, individuals at risk for COVID-19 complications should be started on NKCs immunotherapy and/or antiferrosenescence treatment early after the diagnosis.

Authors statement

All authors contributed equally to this manuscript.

Declaration of Competing Interest

The authors have no conflict of interest and no funding was received for this article.

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