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The potential role of COVID-19 in the induction of DNA damage

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ABSTRACT

The coronavirus disease-2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is challenging global health and economic systems. In some individuals, COVID-19 can cause a wide array of symptoms, affecting several organs, such as the lungs, heart, bowels, kidneys and brain, causing multiorgan failure, sepsis and death. These effects are related in part to direct viral infection of these organs, immunological deregulation, a hypercoagulatory state and the potential for development of cytokine storm syndrome. Since the appearance of COVID-19 is recent, the long-term effects on the health of recovered patients remain unknown. In this review, we focused on current evidence of the mechanisms of DNA damage mediated by coronaviruses. Data supports that these viruses can induce DNA damage, genomic instability, and cell cycle deregulation during their replication in mammalian cells. Since the induction of DNA damage and aberrant DNA repair mechanisms are related to the development of chronic diseases such as cancer, diabetes, neurodegenerative disorders, and atherosclerosis, it will be important to address similar effects and outcomes in recovered COVID-19 patients.

1. Introduction, the COVID-19 pandemic

The disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel zoonotic pathology recognized for the first time in Wuhan, Hubei Province in China in December of 2019 [1]. This disease was named COVID-19 by the World Health Organization and currently it has spread to more than 200 countries with more than 260 million confirmed cases and more than 5 million deaths worldwide (November 2021; https://covid19.who.int/), being declared as a pandemic by the WHO on May 2020 (WHO, May 10th 2020). As this virus will probably become endemic to humans, knowing the long-term consequences of this viral infection will be important in the health management of recovered patients.

The main transmission routes of SARS-CoV-2 have been reported to be from person to person through respiratory droplets, airborne transmission through aerosols and contact with contaminated surfaces [1–3]. People older than 60 years of age, or those with comorbidities such as cardiovascular diseases, type 2 diabetes (T2D), obesity or cancer, have been reported to be at a higher risk to develop more severe COVID-19 [1].

Interestingly, it has been observed that 20–60 % of the patients infected with SARS-CoV-2 are asymptomatic or develop only mild symptoms of the disease [4,5]. Nevertheless, these patients can develop lymphopenia, elevated levels of alanine aminotransferase and C-reactive protein and lung abnormalities such as opacities, shadows, and diffuse consolidation [4]. Moreover, there has been an increase in the number of patients who report symptoms for more than 10 months after the original infection, now recognized by the WHO as long−COVID or post−COVID syndrome [6,7]. Although the prevalence of this persistent syndrome is not completely clear, reports show that it can develop in individuals who were not hospitalized or who exhibited mild symptoms during the acute viral infection [8,9]. Thus, it is relevant to further study the long-term consequences related to the initial viral infection. In this work, we review the information available to date on the potential mechanisms of SARS-CoV-2 to induce DNA damage that may contribute to long-term consequences.

2. The biology of SARS-CoV-2

The SARS-CoV-2 virus is a member of the *Betacoronavirus* genus of coronaviruses [10], which are enveloped, positive-sense and single-stranded RNA viruses [1]. The human virus genome most similar

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to SARS-CoV-2 is SARS-CoV, which caused the SARS pandemic in 2003 [10], and most current knowledge about the biology of SARS-CoV-2 is based on findings attributed to SARS-CoV [10].

Although the precise origin of this virus remains a mystery, it has been described that it shares a high homology with the bat coronavirus RaTG13; while the receptor binding motif (RBM), the critical site in the spike (S) protein that recognizes human ACE2 receptor, is highly homologous to pangolin coronaviruses [11,12]. These homologies suggest that SARS-CoV-2 perhaps originated by a recombination process between bat and pangolin coronaviruses [11].

The SARS-CoV-2 genome is comprised of open reading frames 1a and 1b (ORF1a and ORF1b) that are translated into two large polypeptides that are subsequently cleaved into 16 non-structural proteins (nsp) by the viral papain-like proteases nsp3 and nsp5 [10,13]. Additionally, the viral RNA serves as a template for replication and transcription mediated by the RNA-dependent RNA polymerase (RdRp) nsp12 [13]. These events produce several copies of the genomic RNA (gRNA) and many sub-genomic RNAs (sbRNA) that are translated into the structural proteins: spike (S), envelope (E), membrane (M) and nucleocapsid (N), as well as several accessory proteins [10,13]. Although most of the gRNA codes for nsps, the functions of most of the transcripts remain largely unknown to date.

During viral infection, the S protein of SARS-CoV-2 is cleaved into S1 and S2 subunits by the cell protease furin [1,14]. This cleavage is essential for viral infection, and favors cell-cell fusion events, leading to syncytial formation [1,14]. The S1 subunit contains the receptor binding motif (RBM) that binds to the cell receptor angiotensin converting enzyme 2 (ACE2) [1]. After binding to the ACE2 receptor, the virion is endocytosed and the virus membrane fuses with the cell membrane, releasing the virus into the cell [1]. In order to enter the host cell, the S protein is cleaved by other cell proteases, such as transmembrane protease serine 2 (TMPRSS2), facilitating the endocytosis of the viral particle [1].

After membrane fusion, the viral gRNA is released into the cytosol. This RNA is translated to produce the RNA-dependent RNA polymerase (RdRp) which replicates the virus genome. After the new viral particles are assembled, they are released through exocytosis. Due to the high concentration of furin in the extracellular space in the respiratory system, the viral particles can effectively infect nearby cells [1].

At the clinical level, the infection with SARS−COV-2 typically induces fever, cough and shortness of breath with pathophysiological abnormalities in the lungs. In some cases, the patients develop thrombocytopenia, T cell cytopenia, T cell exhaustion and prolonged prothrombin time. Additionally, in severely ill patients, the infection induces a cytokine storm that leads to an excessive acute pro-inflammatory state that can induce septic shock, multi-organ dysfunction and death, which is known as severe−COVID-19 [1].

In addition to the respiratory symptoms, SARS-CoV-2 infection can also induce neurological and gastrointestinal manifestations [15–17]. Increasing evidence from COVID-19 patients shows that SARS-CoV-2 infects and replicates in endothelial cells from the kidney, lung, heart, and liver [18,19]. The infection of vascular endothelial cells could allow the virus to disperse throughout the body into other organs. Consistent with this idea, the virus was reported to be present in hepatocytes and brain neurons from biopsies of patients who died from COVID-19 [20, 21]. *in vitro* models using human-derived organoids have demonstrated that SARS-CoV-2 infects enterocytes, endocrine pancreatic cells, hepatocytes, cardiomyocytes, brain organoids and dopaminergic neurons [21–24]. Taken together, these studies show that COVID-19 could be a multisystemic disease that could have long-lasting effects in the affected organs. In addition, because the brain is an organ with immune privilege, meaning that the immune system has limited access to this tissue, even foreign antigens do not generally trigger an immune response in this organ [25]. Thus, the ability of SARS-CoV-2 to replicate in the brain of some patients, could lead to a long-term reservoir of the virus which could promote the development of chronic neurodegenerative diseases, similar to what has been shown for herpes viruses [26]. These possibilities should be validated in prospective studies from COVID-19 recovered patients.

3. Viral infections can induce DNA damage by different mechanisms

Maintenance of DNA sequence integrity is crucial to avoid deleterious mutations and to sustain organisms' health [27,28]. On the other hand, mutagenesis is necessary to drive evolution by creating genetic variability, which is particularly advantageous for pathogenic organisms [28]. Because DNA is a reactive molecule that is susceptible to chemical changes due to endogenous and exogenous factors, cells have evolved several DNA repair mechanisms in order to maintain genomic integrity [27]. Genomic instability arises by a variety of different genetic alterations, from base changes, generation of insertions and deletions, and chromosomic rearrangements [28]. These events can be the result of exposure to chemical, physical or biological agents that cause directly DNA damage or interfere with the replication and repair mechanisms [27]. Genomic instability has been implicated in the pathophysiology of several diseases such as cancer, type 2 diabetes (T2D), Alzheimer disease and aging [29–32].

Infectious diseases are a well-known to increases the risks of developing some forms of cancer [33]. The International Agency for Research on Cancer (IARC) includes 10 pathogens as group 1 carcinogens that include bacterial, parasitic and viral infections [34]. It was estimated that 12 % of all human cancers are potentially the result of viral infections [35]. These viral-induced cancers occur principally in immunodeficient or immunocompromised individuals [35]. Interestingly, risk factors associated with severe COVID-19 patients, such as obesity and T2D are often related to an impaired immune system [36].

Viral infections can drive carcinogenic processes by three main mechanisms: a) encoding oncogenic viral proteins, b) causing chronic inflammation or c) causing genotoxic damage [35]. Here we will focus on the last two options, particularly those related to DNA damage that can be induced by chronic inflammation and those related to viral replication processes that can contribute to genotoxicity.

Human papilloma viruses (HPV) are some of the best-known carcinogenic viruses. Several HPV strains that confer a high cancer risk encode oncogenic proteins such as E6 and E7, which induce degradation of the tumor-suppressor proteins p53 and RB1, respectively. The E6/p53 and E7/RB1 complexes result in deregulation of the cell cycle with loss of control of crucial events, such as DNA replication, DNA repair and apoptosis [35]. In turn, these perturbations can result in replication stress, which is characterized by impediments in DNA replication that lead to replication fork stalling and the formation of single strand breaks (ssbDNA) that can generate DNA damage and genomic instability [37].

Hepatitis C virus (HCV) and hepatitis B virus (HBV) induce the development of liver cancer mainly by triggering chronic inflammation [35]. This pro-inflammatory state leads to constant damage in the hepatocytes, cell trans-differentiation and cell damage [38]. Interestingly, HCV is a positive-sense single-stranded RNA virus that can persist as a chronic infection [35,38]. This virus is replicated in the cytoplasm, without being inserted in the nucleus [38]. There is increasing evidence that non-structural proteins of HCV can induce genomic instability and aneuploidies by deregulating the MDM2/p53 pathway [38], indicating that even RNA viruses can directly induce DNA damage and cancer. In this regard, RNA viruses induce DNA damage through different mechanisms, such as the generation of reactive oxygen species, modulation of DNA repair mechanisms and replication fork stress [39].

4. Potential direct mechanisms of coronaviruses to induced DNA damage

Although many aspects of SARS-CoV-2 biology are still far from being known, some hints can be anticipated from the molecular

mechanisms triggered by related coronaviruses such as SARS-CoV and infectious bronchitis virus (IBV). In this section we will describe several potential mechanisms that have been investigated in these coronaviruses that could directly lead to DNA damage in the host. In addition, we discuss the recent analysis of protein-protein interactions between the proteins encoded by the SARS-CoV-2 and human proteins relevant to DNA repair mechanisms.

It has been described that the nonstructural protein nsp13 from both SARS-CoV and IBV interacts with DNA polymerase δ, leading to DNA replication fork stress, DNA damage, H2AX histone phosphorylation and cell cycle arrest [40]. Moreover, the replication efficiency of IBV in lung epithelial cells depends on the induction of DNA repair mechanisms, principally the ATR-dependent pathway [40]. Interestingly, the expression of nsp13 is sufficient to induce fork stress and DNA damage, even in the absence of other viral components or viral replication (Fig. 1) [40]. It is hypothesized that coronaviruses induce DNA replication fork stress to induce cell cycle arrest in the S-phase, which leads to a higher uptake of metabolites required for viral replication [40]. The defects in the replication fork can promote tumorigenesis by inducing genetic instability [41]. DNA polymerase δ is one of the most important enzymes for genome stability; it is the main polymerase involved in the synthesis of the lagging strand during replicative DNA synthesis and is one of several enzymes involved in DNA repair mechanisms [42–44]. Thus, the effects of nsp13 on DNA polymerase δ could contribute not only to direct DNA damage due to replication fork stress, but can potentially also promote genome instability in the presence of other environmental factors, such as air pollution that is associated with the severity of COVID-19 disease and with DNA damage [45,46]. Importantly, the nsp13 of SARS-CoV and SARS-CoV-2 are 99.8 % identical, with only a single mutation of isoleucine 570 to valine [10], indicating that this mechanism could similarly be induced by the novel SARS-CoV-2 coronavirus. Concordantly, the ATR inhibitor berzosertib completely inhibits the replication of SARS-CoV, MERS-CoV and SARS-CoV-2 in epithelial cell lines, demonstrating that the replication of the novel coronavirus depends on ATR-dependent DNA-repair mechanisms [47]. Another recent study found that SARS-CoV-2 infection induces overexpression of ATR and CHK1 in viral host Vero E6 cells [48]. This effect was accompanied with increased phosphorylation levels of ATR, CHK1 and H2AX [48]. At the genomic level, SARS-CoV-2 infection resulted in telomere shortening, which is a documented marker of cell senescence [48]. Thus, demonstrating that replication fork stress and ATR deregulation are common mechanisms shared by coronaviruses, including SARS-CoV-2. In a case report of a COVID-19 patient with Lynch syndrome, which is a colon disease involving a characteristic deficiency of the mismatch DNA repair pathway, the patient was reported to shed viral particles for 54 days, which is considered as a long viral shedding [49]. Thus, this provides another suggestion indicating that the replication potential of SARS-CoV-2 is influenced by the underlying status of DNA repair homeostasis. These studies raise the possibility that if some cells infected by SARS-CoV-2 are not destroyed by the immune system, the expression of nsp13 could promote continuing DNA damage in the long term. It will be interesting in future studies to evaluate whether the long-term expression of nsp13 can be found in recovered COVID-19 patients, or whether the DNA damage induced by this factor is long lasting in patients recovered from COVID-19.

The tumor suppressor protein p53 is a central regulator of genomic stability, cell cycle progress and the suppression of viral replication [50–52]. Thus, this protein is targeted by most oncogenic and non-oncogenic viruses to effectively infect human cells [52,53]. It has been described that the papain-like proteases (nsp3) encoded by SARS-CoV, MERS-CoV and the HCoV-NL63 coronaviruses stabilize the ubiquitin ligase ring-finger and CHY zinc-finger domain-containing 1 (RCHY1), which mediates the ubiquitination of p53, promoting its degradation (Fig. 1) [54]. It is noteworthy that the nsp3 from SARS-CoV has a higher effect over p53 degradation, due to the presence of a SARS-unique domain, compared with the nsp3 protein without this domain [54]. Since nsp3 from SARS-CoV-2 and SARS-CoV have an identity/similarity of 76.0 % and 91.8 % respectively [10], it can be expected that the extent of p53 downregulation could also be similar between these viruses, but this possibility needs to be addressed in future studies. The infection with SARS-CoV in Vero E6 cells results in an increased expression of a truncated p53 isoform, that impairs the function of WT p53 [55]. These results further suggest that in addition to decreased p53 abundance, the functionality of the remaining p53 could

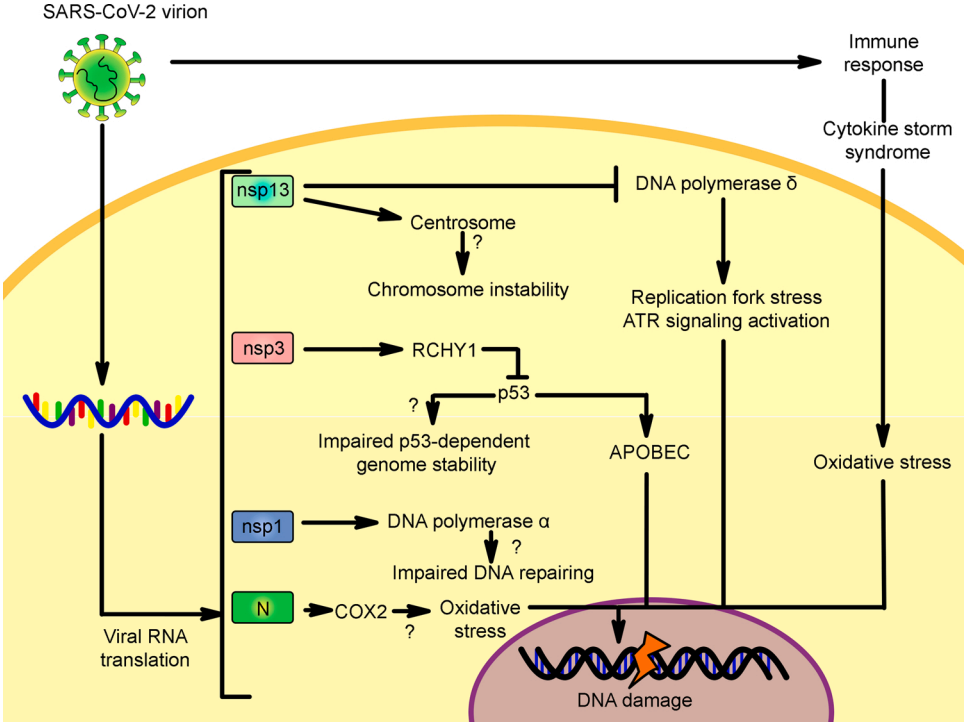

Fig. 1. Potential mechanisms triggered directly by SARS-CoV-2 proteins and indirectly through the immune system. The mechanisms are based on the knowledge of proteins encoded by the SARS-CoV-2, SARS-CoV. Infectious bronchitis virus and the MERS-CoV. Since the orthologous proteins encoded in the SARS-CoV-2 genome share a high percentage of identity/similarity, it is possible that these mechanisms are induced by this newly described virus. Nsp13: non-structural protein 13, nsp3: non-structural protein 3, nsp1: non-structural protein 1, N: nucleocapsid, RCHY1: ring-finger and CHY zinc-finger domain-containing 1 ubiquitin ligase, Cox2: cyclooxygenase 2, APOBEC: apolipoprotein B mRNA editing enzyme catalytic polypeptide-like family of cytidine deaminases.

be impaired in cells infected by SARS-coronaviruses. Impairment of p53 functions is of particular concern because during severe COVID-19 illness, the patients develop a pro-oxidant state that is also correlated with sustained oxidative DNA damage (discussed below) [56,57], which could increase the probability of a blunted response to DNA damage. Notably, an increase of p53 degradation and the resultant impairment of its normal cell functions are common characteristics of other viruses such as Epstein-Barr virus and human herpes simplex virus-1 [52]. Interestingly, these viruses have also been associated with the development of chronic diseases, such as cancer and Alzheimer's disease, which can be related to DNA damage and genomic instability [58,59]. Therefore, the effects of SARS-CoV-2 infection on p53 stability, the possible link with genome instability related to p53 impairment, and the potential for enhancement of later life diseases such as cancer and neurological diseases following COVID-19 need to be addressed in future studies.

In addition to its role in coordinating the DNA damage response, p53 regulates the expression of the APOBEC family of cytidine deaminases. These enzymes have been shown to be induced after interferon (IFN) stimulation in response to viral infections, inducing mutations in the viral and host DNA [53]. Thus, the deregulation of p53 by coronavirus infection could lead to alterations in the expression of these enzymes, potentially resulting in genetic instability. Interestingly, in MRC-5 cells infected with the human coronavirus HCoV-229E there was an upregulation of the APOBEC3B gene [60]. Moreover, 41 % of the base mutations in SARS-CoV-2 correspond to the mutational signature of APOBEC cytidine deaminases, in comparison with 24 % of the base mutations observed in HCoV-229E [60]. Thus, the results support the concept that coronavirus infection, including SARS-CoV-2 effectively results in deregulation of these cytidine deaminase enzymes.

The nucleocapsid (N) protein of SARS-CoV induces the overexpression of the cyclooxygenase-2 (COX2) in lung cells [61]. Moreover, N protein acts as a transcription factor that binds directly to regulatory elements containing NF-κB and C/EBP binding sites in the COX2 gene promoter (Fig. 1) [61]. COX2 is an inducible enzyme with pro-inflammatory and pro-oxidant functions that promotes lipid peroxidation even in non-exposed cells through bystander effects [62,63]. This enzyme promotes genomic instability and DNA damage by inducing DNA adducts and by altering the glutathione levels in the cells [62]. Additionally, COX2 produces prostaglandin E_2, which is a pro-inflammatory factor that can exacerbate the pro-oxidative conditions and the induction of DNA damage [62]. Interestingly, it has been shown that COX2 is overexpressed during carcinogenic processes induced by other pathogens such as *Bacteroides fragilis*, which is a risk factor to the development of colon cancer [64]. Future studies are needed to assess whether COX2 is induced in the tissues from COVID-19 patients, and to determine if the expression levels of this enzyme correlate with oxidative DNA damage.

The description of a high-confidence interactome between the proteins encoded in the genome of SARS-CoV-2 with human proteins determined through mass spectrometry suggest additional mechanisms for SARS-CoV-2-induced DNA damage [65,66]. For example, the nsp1 protein has been found to interact with the four subunits of the DNA polymerase α (Fig. 1) [66]. This enzyme, in addition to its fundamental role in the initiation of the DNA synthesis, is involved in cell cycle regulation and DNA repair mechanisms [67]. Another example is the finding that nsp13 from SARS-CoV-2 interacts with several proteins of the centrosome complex (Fig. 1) [66]. Disruption of centrosome duplication and structure can lead to genomic instability by promoting aneugenic mechanisms leading to alterations of chromosome number and structure, which are common features of human malignancies [68]. Remarkably, the nsp13 encoded in SARS-CoV and IBV is the same protein noted to be responsible for replication fork stress and ATR activation [40], indicating that this protein can have multiple important effects on the host genome stability. Although the meaning of these interactions still remains hypothetical, these studies highlight the possibilities for SARS-CoV-2 to impair DNA repair mechanisms, induce DNA damage, and induce oxidative stress in human cells.

5. Potential indirect mechanisms of SARS-CoV-2 induced DNA damage: Aberrant inflammation, immune response and oxidative damage

The most severe forms of COVID-19 have become associated with a deregulated pro-inflammatory response known as cytokine storm syndrome [69–71]. Although interleukin-6 (IL-6) is the main cytokine overexpressed in severe and critical COVID-19 patients, the levels of this factor are several orders of magnitude lower than those observed in other inflammatory syndromes such as acute respiratory distress syndrome (ARDS), cytokine release syndrome (CRS) and overt sepsis [69]. Other typical cytokines involved in the cytokine storm syndrome induced by ARDS, CRS or sepsis are less abundant in COVID19 patients (such as IL-8, TNFα, IFNγ and sIL-2R), raising questions about their relevance in the outcome of the COVID-19 patients [69]. On the other hand, the levels of C-reactive protein are substantially higher in COVID-19 patients than in other cytokine storm syndromes [69].

C-reactive protein is produced by the liver in response to tissue damage, infections, and inflammatory signals. This protein binds to phosphatidyl choline in the membranes of the dying cells and bacteria, inducing their phagocytosis by circulating macrophages and promoting systemic inflammation [72]. It has been found that high levels of C-reactive protein are associated with high levels of oxidative damage in the DNA of patients with psoriasis, obesity, pancreatic cancer, and cardiovascular diseases [73–76].

Moreover, chronic inflammation is associated with the production of reactive oxygen species that can promote the development of some types of cancer, insulin resistance and vascular lesions [77–79]. In COVID-19 patients, serum levels of glutathione and total thiol are decreased, while levels of superoxide dismutase, catalase, malondialdehyde (a marker of oxidative stress and lipoperoxidation) and the total oxidant status are increased [57,80–82]. Oxidative stress levels correlated with blood oxygen saturation levels, disease severity, prognosis, and with the virus variant that was causing the infection [57,80,82,83]. Mechanistically, an analysis of transcriptome changes observed in different data sets from blood cells, lung biopsies or leukocytes from healthy subjects and COVID-19 patients showed that there is a significant upregulation of pro-oxidant genes, principally the myeloperoxidase and calprotectin genes [84]. Another study found that the peptides derived from the S protein of SARS-CoV-2 increased the levels of nitrites, hydrogen peroxide and reactive oxygen species (ROS) as well as upregulated the activities of superoxide dismutase and catalase in a tadpole model [85], indicating that the S protein itself can induce oxidative stress in animals. Altogether, these studies suggest that oxidative stress plays an important role in COVID-19 pathogenesis, and all of these clinical observations require mechanistic research follow up.

Oxidative stress results from the imbalance between ROS production and the levels of antioxidant molecules in cells [86]. This pro-oxidant state results in the damage of macromolecules such as lipids, proteins and nucleic acids (Fig. 1) [86]. In the DNA, oxidative stress can induce several types of damage, including single- and double-strand brakes, DNA-protein crosslinks and base and sugar oxidation products, such as guanine oxidized species (GOS) [86–88]. A study assessed the presence of GOS in the serum of critical COVID-19 patients from intensive care units [56]. The authors reported that the GOS levels in the serum from non-surviving COVID-19 patients were higher than in those that survived, suggesting that oxidative DNA damage could be a predicting factor of death by COVID-19 [56]. However, the study lacked groups of asymptomatic COVID-19 patients and control groups of non-infected subjects that are necessary to demonstrate that oxidative DNA-damage is present in COVID-19 patients, regardless of the severity of the disease. Another study compared serum malondialdehyde and GOS levels for 14 days in hospitalized versus non-hospitalized COVID-19 patients

[89]. The authors found that malondialdehyde peaks at the time of hospitalization, rapidly dropping during the time-course analyzed, while the GOS peaked at 7 days after admission [89]. These findings suggested that oxidative stress precedes DNA damage during COVID-19 pathogenesis. Intriguingly, malondialdehyde levels were higher in the non-hospitalized patients, while the hospitalized patients had higher levels of serum GOS; but the authors did not correlate this finding with oxygen administration or later disease severity [89]. This later work suggests that in severe COVID-19, there is a higher risk to developing DNA oxidative damage, perhaps in part due to sustained oxygen supplementation during in-hospital patient care. Likewise, a study aimed in determining DNA fragmentation in sperm cells, and semen quality of patients with mild cases of COVID-19, found that DNA fragmentation in the sperm cells and oxidative stress markers were higher at 14 days after diagnosis, compared with levels in the same patients 120 days after diagnosis [90,91]. However, as in the previous studies, this work lacked a control group of non-infected subjects. Thus, future studies comparing markers of oxidative DNA-damage between non-infected subjects and patients from the whole spectrum of COVID-19 patients undergoing both hospitalization and home recovery are needed to determine the extent of oxidative DNA damage induced by COVID-19 infection and/or treatment.

Oxidative DNA damage has long been associated with increased risks of developing neurodegenerative diseases and several types of cancer [59,86,92]. This raises the possibility that severe COVID-19 patients, who have a pro-inflammatory and pro-oxidative states, could also have higher risks of developing other chronic diseases in the long term, and that perhaps in cases of patients with comorbidities, these comorbid diseases could be worsened by SARS-CoV-2 viral infection. Future studies are needed to address the risks of developing such pathologies in both ailing and recovered COVID-19 patients.

6. Concluding remarks

The global SARS-CoV-2 pandemic is challenging every aspect of human society, and the short and long-term impacts on human health are still new and uncertain. The risk of later development of chronic diseases in recovered COVID-19 patients is not yet known. Coronaviruses of the same family as SARS-CoV-2 can induce DNA damage and impair DNA repair mechanisms, thus fostering genome instability. It is known that DNA damage and aberrant repair mechanisms are implicated in the pathogenesis of many chronic diseases such as cancer, obesity, diabetes, atherosclerosis and metabolic syndrome. These potential outcomes highlight the need to evaluate the long-term effects of this novel viral disease in the recovered COVID-19 patients as well as in asymptomatic but infected individuals.

Author statement file

Pablo Pánico: Conceptualization, Investigation, Writing-original draft, Visualization **Patricia Ostrosky-Wegman:** Conceptualization, Investigation, Writing-Review and Editing, Funding acquisition **Ana María Salazar:** Conceptualization, Investigation, Writing-Review and Editing, Supervision, Project administration

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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