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Review Article

Towards SARS-COV-2 Effects on the Genetic Apparatus of Target Cells

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Abstract

Integrity of a cellular genome is under constant attack from DNA-damaging agents. These include endogenous cellular compounds, as well as exogenous agents such as RNA viruses. The latter can cause significant DNA damage, even if viral replication occurs exclusively in the cytoplasm. The DNA damage response (DDR) comprises sensors, transducers and effectors, which together form a signaling cascade involving complex protein-protein interactions and post-translational modifications. Initiation of this cascade leads to cell cycle arrest and activation of DNA repair pathways. For example, the kinases ataxia telangiectasia mutated (ATM) and DNA-dependent protein kinase (DNA-PK) are primarily-activated by double-strand breaks (DSBs), whereas ataxia telangiectasia and Rad3-related (ATR) kinase is stimulated at regions of single-stranded DNA (ssDNA) that arise at DSBs or stalled replication forks.

This review summarizes known effects of SARS-CoV-2 and other coronaviruses on the genome integrity of infected cells and the induction of DNA damage responses. Notably, SARS-CoV-2 has been suggested to affect DNA integrity of both somatic and germ cells. One focus of this article will be on the formation of so-called "virus factories" near microtubules and their effects on cell division and chromosome segregation. Furthermore, the effect of co- or superinfections with other viruses (e.g., influenza, rhino-, entero-, noroviruses, etc.) and a potential exacerbation of DNA damage will be presented.

Elucidating the interactions of RNA viruses with host DNA damage responses and the induction of genomic instability will not only provide important insights into viral pathogenesis, but may also help to advance current therapeutic approaches.

Keywords: SARS-CoV-2; Target Cells; Genetic Instability; Chromosome Damage

Abbreviations

CoV: Coronaviruses; MN: Micronuclei; ATM: Ataxia Telangiectasia Mutated Kinase; Chk2: Checkpoint Protein; DSBs: DNA Double-Strand Breaks; ACE2: Angiotensin-Converting Enzyme 2; TADs: Topologically Associated Domains; VP: Viral Protein

Introduction

Although there is nothing surprising in the occurrence of emerging viral infections, no country was ready to adequately respond to the ongoing SARS-CoV-2 pandemic. Emerging viruses have appeared at different times in different regions of the planet. Recent examples include diseases caused by Zika, Ebola, Nipah, and Hendra viruses. The current SARS-CoV-2 pandemic has illustrated once again the imperfection of health care systems around the world.

Coronaviruses (CoVs) are the largest group of viruses belonging to the order *Nidovirales* and suborder *Cornidovirineae*. To date, 8 suborders have been established under the *Nidovirales* order: *Abnidovirineae, Arnidovirineae, Cornidovirineae, Mesnidovirineae, Monidovirineae, Nanidovirineae, Ronidovirineae, and Tornidovirineae* (Walker PJ, Siddell SG, Lefkowitz EJ., *et al*.

2019). These 8 suborders contain 14 viral families, 25 subfamilies, 39 genera, 65 subgenera, and a total of 109 viral species (Zhou Z, Qiu Y, Ge X., 2021). Notably, coronaviruses are not new human pathogens. Two species of human coronaviruses (HCoV) have already been detected in humans more than 50 years ago: HCoV-OC43 (Organ Culture 43) in 1967 (McIntosh K, Dees JH, Becker WB., *et al*. 1967) and HCoV-229E in 1966 (Hamre D, Procknow JJ,1966). Two additional species (HCoV-NL63 (Netherlands 63) and HCoV-HKU1 (Hong Kong University 1)) that have also been circulating in humans for many years were described in 2004 and 2005, respectively (van der Hoek L, Pyrc K, Jebbink MF., *et al*. 2004; Woo PC, Lau SK, Chu CM., *et al*. 2005). These four HCoV species are responsible for mild seasonal infections of the upper respiratory tract and usually cause minor symptoms (McIntosh K, Dees JH, Becker WB., *et al*. 1967). In contrast to the endemic coronaviruses OC43, 229E, NL63 and HKU1, SARS-CoV, MERS-CoV and SARS-CoV-2 are significantly more pathogenic in humans. Still, SARS-CoV, MERS-CoV and SARS-CoV-2 are characterized by different infection fatality rates: 10% for SARS-CoV (2002-2003), 35% for MERS-CoV (2012) [10], and 4.08-15% [13] or 37% for SARS-CoV-2 [10]. While SARS-CoV, MERS-CoV, and SARS-CoV-2 share many characteristics such as the induction of severe respiratory illness, the respective illnesses have distinctive traits. For example, there are differences in the incubation periods (the median of this period is 4 days for SARS-CoV (Lessler J, Reich NG, Brookmeyer R., *et al*. 2009), and 5.2 days for MERS (Memish ZA, Perlman S, Van Kerkhove MD., *et al*. 2020). Moreover, acute kidney injury is detected as one atypical symptom in more than half of all MERS patients while this is not the case for SARS-CoV and SARS-CoV-2 infections.

A characteristic feature of coronaviruses is their wide range of natural hosts in combination with a pronounced species restriction of pathogenicity. Apart from humans, they have also been found in many animal species (e.g., pigs, mice, bats, rats, minks, camels, horses, cats, dogs, cattle, birds, etc.) [1]. The host cell and tissue tropism of coronaviruses, including SARS-CoV-2, is also quite broad, ranging from the intestines and respiratory tract to nerve cells [7,15,37]. As a consequence, coronaviruses can cause hepatic, enterotropic, pneumotropic and neurotropic infections of varying severities. According to their ability to infect different organs, coronaviruses can be classified as pantropic viruses. Diseases caused by coronaviruses are mostly acute, although chronic and latent forms of infection are also possible, also in the case of SARS-CoV-2 (Geng J, Yu J, Lu T., *et al*. 2020; Logue JK, Franko NM, McCulloch DJ., *et al*. 2021). Persistent infection may occur in some immunocompromised individuals, such as those with primary immunodeficiency or those receiving immunosuppressive therapy. While some authors propose that "Long-COVID" is the result of a latent, chronic SARS-CoV-2 infection in extrapulmonary tissues, others emphasize that chronic persistent infection should not be confused with "Long-COVID", where infection is cleared rapidly, yet symptoms persist (Harari S, Tahor M, Rutsinsky N., *et al*. 2022). In a few cases, persistent, but asymptomatic SARS-CoV-2 infection of people with normal immune status have also been described (Proal AD, Van Elzakker MB, 2021).

As a cytopathic virus, SARS-CoV-2 frequently results in the death of virus-infected cells. Notably, however, not all SARS-CoV-2 infected cells are killed by the virus (Zhao H, Lu L, Peng Z, Chen LL., *et al*. 2022), a feature that depends on the host cell type and many other factors. This is important, because negative changes in the genome can occur in these cells and they can pose a threat to the physiological function of the tissues of the infected organism.

The first stage of coronavirus infection involves binding of the viral spike (S) protein to cellular entry receptors. For HCoV-229E, this receptor is human aminopeptidase N (APN) (Vijgen L, Keyaerts E, Zlateva K., *et al*. 2004), while angiotensin-converting enzyme 2 (ACE2) mediates entry of HCoV-NL63, SARS-CoV, SARS-CoV-2 (Tay MZ, Poh CM, Renia L., *et al.* 2020), and dipeptidyl peptidase 4 (DPP4) is bound by the spike protein of MERS-CoV. Interestingly, SARS-CoV-2 spike binds to ACE2 with a ten times higher affinity than SARS-CoV spike (Hoffmann M, Kleine-Weber H, Schroeder S., *et al*. 2020). All these spike-receptor interactions affect the tropism and pathogenicity of the virus. The ACE2 receptor has been detected in various human cells and tissues (e.g., oral and nasal mucosa, nasopharynx, lung, stomach, small intestine, colon, skin, lymph nodes, thymus, bone marrow, spleen, liver, kidney, testis, pancreas, heart, placenta and brain) (Hamming I, Timens W, Bulthuis ML., *et al*. 2004). In all organs, the ACE2 receptor was also present in arterial and venous endothelial cells and arterial smooth muscle cells. The presence of ACE2 in the epithelia of the lung and small intestine might provide possible routes of entry for SARS-CoV (Hamming I, Timens W, Bulthuis ML., *et al*. 2004) and SARS-CoV-2 (Scialo F, Daniele A, Amato F., *et al*. 2020).

Notably, it is still not entirely clear how the virus can affect the genetic apparatus of infected cells and uninfected bystander cells. This review will address several important (but frequently unanswered) questions: What changes at the genetic level (chromosomal, genomic, etc.) result from the interaction of the virus with a cell? How does SARS-CoV-2 affect genetic stability and proper mitosis of infected cells? Do all cells of an infected host undergo the same changes under the influence of the virus? Does a person's sex affect the response of infected cells to the virus? Do somatic and germ cells of the same infected person react in the same way? How do changes occur in these cells depending on the severity and dynamics of infection? Are these processes the same in different individuals? What are the dynamics of these changes depending on the time of contact of the virus with the susceptible cell? How do other host cells, which are considered insensitive to viral infection, react to viral aggression?

It is known that the process of mutation is inherent to all living organisms, occurs spontaneously and can be induced by various natural and artificial factors. Mutagenic factors can be subdivided into three groups: 1) physical factors (X-rays, γ-rays, other types of ionizing radiation, infrared radiation, UV rays with a wavelength of 2500-2800 Å, temperature, ultrasound, mechanical action, corpuscular particles - electrons, protons, neutrons, etc.), 2) chemical factors, and 3) biological factors (aging, viruses, etc.).

Two approaches are used to identify mutagenic factors influencing the heredity of living organisms - ecogenetic and genotoxicological, using different test systems, of which there are more than a hundred, both *in vitro* and *in vivo*. Each method used in genetic monitoring has its disadvantages and advantages. To identify different types of damage, comprehensive genotoxicological studies are performed. This is a kind of sieve that is likely to detect mutagens and their effects. Detecting and accounting for the frequency of gene mutations is a challenging task due to many factors. Most mutations are recessive, a significant number are predominantly lethal and may exist in diploid cells due to the functioning of their normal allelomorphs. The vast majority of mutations are semi-lethal.

Not all primary DNA damage is repaired by the cellular repair machinery. However, mutations that are not repaired do not necessarily remain as they may be eliminated together with the mutated cell, e.g. via apoptosis or necrosis. Changes in chromosome structure are characterized by the appearance of deletions, duplications, inversions, insertions and translocations. The frequency of chromosomal mutations was previously recorded by cytological methods in the control of mitotic pathologies. Point mutations are more common than chromosomal aberrations. About half of all mutations occur in the form of instability, which replicates and can be inherited in populations indefinitely. Thus, identifying mutagenic factors and predicting the risk of their effects is important in studying the functioning of mammalian cell genomes, including humans, needed to maintain homeostasis of cells and organisms, and finding ways to reduce the negative effects of genotoxicological stress.

DNA damage may contribute to the pathogenesis of RNA virus-induced disease by triggering apoptosis, stimulating inflammatory responses, and/or introducing deleterious mutations that may even increase the risk of oncogenesis. Thus, a better understanding of the interactions between RNA viruses and host DNA damage responses will not only shed light on mechanisms underlying the development of viral disease, but also provide important insights into cellular responses to viral infection.

The reaction of cells to viral exposure or infection is a complex process that develops over time and comprises several phases that influence each other. The cell's response to stimuli is an oscillatory process that runs at different speeds, depending on the type and strength of the stimulus. Cytopathic processes in viral infections are diverse. They are determined by both the virus and the cells. It should also be kept in mind that the mutagenic potential is different for different types of viruses, and sometimes for strains of the same virus species. Increased cell mutability usually results in increased virus mutability, which in turn allows the virus to avoid the intracellular immune mechanisms of the host. Since the virus strictly depends on the metabolism of its host cell, mutagenesis of the host cell will inevitably also affect the viral genetic material.

When studying mutagenesis, including infectious mutagenesis, it is important to determine the condition and cell cycle phase of the cell (undergoing viral infection). Duration of cell cycle phases varies considerably in different cell types. In some internal organs in adults, as for example, lung, kidney, skin fibroblasts, liver, some cells divide only occasionally when needed to replace cells that have been lost because cell death or of damage. These cells enter a quiescent stage called G0 phase, where they remain

metabolically active but no longer proliferate unless called on to do so by appropriate extracellular signals (Cooper. GM, 2000). Many cells spend most of their time at rest (i.e., in the G0 phase) [29]. Cells that are at rest (after the end of DNA synthesis) are present in each cell population but the total number of them depends on the cell type. During this period of rest, cells are smaller than cells in the G2 phase, and characterized by their least condensed chromatin state. The degree of nuclear chromatin condensation and change in its shape during cell cycles is very important in viral interactions. Chromosomes become visible during prophase when chromatin condensation begins [3]. Recent advances in the molecular mechanisms of mitotic of chromatin states and its changing are described in more detail in some reviews [2,3]. The ratio of the total DNA length to the length of the chromosome and density of DNA packaging (condensation) plays an important role in DNA damage.

Reactive oxygen species (ROS), appearing as a result of RNA virus infections, are often the source of endogenous DNA damage. During replicative cycles of RNA viruses, they can potentially inflict of DNA damage through different mechanisms. Recently, for some RNA viruses these mechanisms described [9,12,30,33,41,43,44,46]. Enhanced of cellular stress responses, causes by SARS-CoV-2 infection, can induced by changing function as mitochondria's, as proteasomes, as to alterations of redox balance in infected cell. Increasing of lipid peroxidation, ROS and IL-6 production can lead to cell and DNA damage (Nasi A, McArdle S, Gaudernack G., *et al*. 2020).

For example, of a coronavirus inducing DDR is porcine epidemic diarrhea virus (PEDV), which causes enteritis in pigs with acute diarrhea, vomiting, dehydration, and high mortality rates mainly in neonatal piglets, rarely in pregnant sows (Jung K, Saif LJ, Wang Q., 2020; Song D, Moon H, Kang B., 2015). This virus, an *Alphacoronavirus* from the family *Coronaviridae*. It has caused significant economic losses in many countries and has increased mortality among seronegative newborn piglets, resulting in the loss of 10% of the pig herd in the USA (Song D, Moon H, Kang B, 2015).

A recent study showed that PEDV induces DDR in infected cells [24]. The researchers consider that activation of ATM-Chk2 signaling may influence on induces this DDR because inhibition of ataxia telangiectasia mutated kinase (ATM) or checkpoint protein (Chk2) decrease of early stage of PEDV infection. Increasing of intracellular ROS production correlated with increased of ATM signaling that activated by PEDV. Interestingly, that "PEDV infection leads to a unique histone H2AX (referred as γH2AX) staining pattern (that differs from the typical DDR foci), including phase I (nuclear ring staining), II (pan-nuclear staining), and III (co-staining with apoptotic bodies), which highly resembles the apoptosis process. That is why PEDV-induced phosphorylation of γH2AX depends on the activation of caspase-7 and caspase-activated DNAse (CAD) [24]. PEDV replication attenuation appearing as a resulting from oppression of γH2AX. The authors concluded that "PEDV induces DDR through the ROS-ATM and caspase7-CAD-γH2AX signaling pathways to foster its early replication" [24].

Breaks in both strands of the DNA double helix (DSBs) in every nucleated vertebrates' cell are considered a fairly common occurrence, occurring daily and may accumulate up to ten DSBs [17], according to other sources about 10-50 DSBs formed daily in one human cell [22,42]. With regard to the daily formation of single-strand breaks (SSBs) in mammalian cells, their number is estimated to be ~55,000 [8,33]. The mechanisms of formation of both SSBs [8] and DSBs [5,24] in different cell types, cell cycles and chromatin structure have been studied and well summarized, for example, in review of Cannan W. and Pederson D. (2016). An early sensor of DSBs is thought to be the MRE11-RAD50-NBS1 complex (Bian L, Meng Y, Zhang M, Li D, 2019), which plays an important role in DNA damage recognition and repair and which activates ATM ("master controller of signal transduction") [38]. For the preventing of mutated DNA (after its damage) replication in cell have three major checkpoints (the G1/S, the S-phase, and the G2/M) with different functions and mechanisms that initiate arrest of cell cycle [12,31,38] and activated by different kinases [33,45]. The defects in cell cycle checkpoints or in cell proliferation can induce of DNA damage too.

Other coronaviruses can induce of cell cycle arrest, for example, the murine hepatitis coronavirus and SARS-CoV. In experiments in HEK 293, Vero cells SARS-CoV blocking of G0/G1 phase through the cyclin D3/pRb pathway after 24 to 60 h of virus influence that has been well described by Yuan., *et al*. (2006).

Many RNA viruses have evolved mechanisms to inhibit or delay apoptosis, as apoptosis, which occurs prior to the production of infectious progeny by the virus, usually has a deleterious effect on the spread of the virus [33]. For example, the hepatitis C virus (HCV) core protein promotes cell survival by activating the NF-kB mechanism, which may contribute to the oncogenic potential of this virus (You LR, Chen CM, Lee YH, 1999).

Those viruses that cause DNA damage in the early stages of replication often require disruption of pro-apoptotic signals in order to successfully complete replication. Regardless of its effect on the viral replication cycle, apoptosis can make a significant contribution to viral pathogenesis. However, some viruses induce apoptosis and use it for their maturation and proliferation [33].

DDR pathways have mainly been studied in the context of the effects of DNA viruses, and - understandably - research has focused on species of human health concern. Studies investigating the interaction between RNA viruses and their induced DDR are few and to date have mainly focused on HCV, retroviruses HIV-1 and human T-cell lymphotropic virus 1 (HTLV-1) [13,30,39]. Here we also summarize data on other RNA viruses that are known to affect the genetic apparatus of host cells. Newcastle disease virus and Sendai virus caused chromosome damage (up to pulverization) in Hela cells and human embryonic fibroblasts with an increase in tetraploid cells [9]. In addition, arboviruses, such as Japanese encephalitis [50], tick-borne encephalitis and West Nile Fever viruses have caused chromosomal abnormalities and/or altered cell division cycles [49]. In addition, infectious bronchitis virus of chickens, influenza A virus, Chikungunya virus, Sindbis virus, La Crosse virus, Rift Valley fever virus and avian reoviruses have been shown to interfere with DDR [16,33], whereas Western equine encephalitis virus caused no mutagenic effects [49]. Since the mutagenic effect of RNA viruses raises many questions, it is necessary to find out how RNA viruses affect nuclear material and in which phase the cell is most sensitive to viruses. It is likely that the negative effect of viruses on DNA is most pronounced during chromatin decondensation, when the DNA is least protected.

A prolonged quiescent state of cells changes their sensitivity to damaging agents. Stimulated cells require more time for the transition from the quiescent state to the S-phase than constantly proliferating cells that have completed mitosis. During the transition to rest the antigenic structure of the cell surface also changes. The homeostasis of each cell is maintained by changing the rate of synthesis and degradation in accordance with changes in environmental conditions. The cell is a highly dynamic system, which is characterized by continuous change of the rate of processes occurring in it in accordance with general conditions of organism existence at each given moment of time. Under external pathogenic influences the intensity of intracellular processes may increase considerably.

A better understanding of the interaction of coronaviruses with the DDR pathway is needed. Of particular interest is the effect of COVID-19 vaccines (e.g. mRNA vaccines) on the genetic apparatus of cells. SARS-CoV-2 vaccines have been shown to induce increased oxidative stress in healthy individuals 24 h after vaccination. Consistent with oxidative stress being a major contributor to DNA damage, a significantly higher level of DNA damage was observed in vaccinated people compared to people before vaccination. However, the DNA damage was successfully repaired in these individuals 14 days after vaccination (Ntouros PA, Vlachogiannis NI, Pappa M., *et al*. 2021).

RNA viruses cause not only chromosomal instability and induction of DDR, but also the appearance of micronuclei (MN). Notably, high levels of MN in lymphocytes correlate with the frequency of micronuclei in other tissues of the body (Ceppi M, Biasotti B, Fenech M, Bonassi S, 2010; Kirsch-Volders M, Fenech M, 2021), as well as with an impaired immune response and increased susceptibility to RNA-virus-induced diseases. The formation of MN can be induced indirectly, through the production of inflammatory cytokines (Kirsch-Volders M, Fenech M, 2021). This has led the authors to hypothesize that people with an increased frequency of micronuclei in their cells are more susceptible to RNA virus-induced disease. Moreover, the degree of cytokine production and pro-inflammatory response to RNA virus infection is increased and possibly exceeds threshold levels which may be critical in people with elevated levels of MN in affected organs. Given this hypothesis, increased and prolonged expression of cytokines may cause deleterious immune activation and hence disease symptoms. It has been hypothesized that reducing the production of MN, for example by improving diet and lifestyle factors, may increase resistance to infection by RNA viruses and reduce the production

of inflammatory cytokines (Kirsch-Volders M, Fenech M, 2021). Ineffective DNA replication or its repair can form fragmented chromosomes that have fallen into the micronuclei. Premature condensation and ligation of newly synthesized DNA sites can also cause this phenomenon. Here is speculation about the formation of a hypermutated chromosome that may arise from the joining in the nucleus of fragments of one or more severed chromosomes (Bell JC, Straight AF, 2015; Ly P, Brunner SF, Shoshani O., *et al*. 2019).

The detailed mechanisms of MN formation are not yet known, although it has been suggested that they may be due to several causes. One is an incomplete mitotic apparatus (due to defective proteins); another is the loss of a complete centromere in the chromosome structures. Individual chromosomal structures may be surrounded by a micronucleus membrane and thus physically separated from the nucleus (Kirsch-Volders M, Fenech M, 2021). An ineffective immune response can result from an increased frequency of micronuclei in immune cells, which contributes to the development of RNA virus infections. If the two phenomena combine: an increase in the frequency of micronuclei in immune cells in parallel with an increase in the frequency of micronuclei in organ tissue cells when RNA virus infections occur (including SARS-CoV-2), this could presumably weaken the immune response and worsen the pro-inflammatory response (Ren H, Ma C, Peng H., *et al*. 2021).

Nuclear structures affected by coronavirus infections

Of particular interest is the spatial interaction between SARS-CoV-2 and host cell genomes and how this affects the pathology caused by the virus. Notably, mutations can be caused by a direct mutagen action on the gene structure or result from disruption of replication, recombination and transcription. Interestingly, different genes are characterized by different sensitivity to mutagenic factors [11,32,34,48]. Induced mutagenesis, including that caused by viruses, depends on the dose and timing of exposure to the mutagenic agent and the presence of modifying and multiple host factors. It can occur immediately after exposure to mutagens or have a delayed (cumulative) effect. Point mutations account for the vast majority of mutations and can be dominant, semi-dominant or recessive. Mutagens, including viruses, can affect people differently depending on their sex and age. The study of somatic mutations has revealed not only the mutagenic effect, but also predicted the carcinogenic risk of various factors depending on the strength of the factor and allowed the prediction of the actual risk. The risk of mutagenic effect can be considered at the individual or population level. The same mutational risk may be negligible for an individual, but in populations the effect can be pronounced and amplified.

Most RNA viruses are known to replicate exclusively in the cytoplasm, suggesting that the impact of the viral replication cycle on the nucleus may be less severe than in the case of many DNA viruses. However, proteins encoded by RNA viruses are often transferred to the nucleus, where they can disrupt cellular functions and suppress the antiviral response [33]. In the nucleus of SARS-CoV-2 infected cells (Hep-2) some viral proteins are found: Nsp1, Nsp5, Nsp9, Nsp13, Nsp14 and Nsp16 (Shi FS, Yu Y, Li YL., *et al*. 2022; Zhang J, Cruz-Cosme R, Zhuang MW., *et al*. 2020; Fung SY, Siu KL, Lin H., *et al*. 2022). The smallest of the major structural proteins of SARS-CoV-2 (envelope (E) protein) was also detected in the nucleus [47]. Repair of damaged DNA can be prevented too by the SARS-CoV-2 spike (S) protein, which may also be located in the nucleus. Its overexpression interferes with the repair of damaged DNA in cells and impairs cell proliferation [19]. One of the recalled publications described a potential molecular mechanism by which SARS-CoV-2 S protein can interfere with adaptive immunity and highlighted the danger of potential side-effects of vaccines based on the full-length S protein (Jiang H, Mei YF, 2021; Barberis E, Vanella VV, Falasca M, Caneapero V., *et al*. 2021).

Infectious bronchitis of chickens caused by coronavirus (IBV) remains a major cause of economic losses in the poultry industry (Cavanagh D., 2007). IBV infection leads to the cell cycle arrests at the S and G2/M phases and to DNA damage [44]. Established *in vitro* that both coronaviruses (IBV, SARS-COV-2) have a similar RNA replication-transcriptional complex [20]. The S-phase arrest in IBV-infected cells induce through DNA replicative stress [44] which is caused by an interaction between IBV non-structural protein 13 (Nsp13) and DNA polymerase δ, and ATR activation [28,33,44]. This promotes a favorable condition for both viral RNA and cellular DNA replication [16,28,40]. It is possible that IBV may mediate translocation of host factors between viral replication sites and the nucleus [16,33,43,44]. That is why several cell lines (Vero, HeLa, H1299) were selected to determine DNA damage and the state of the cell genome under the influence of IBV [44]. All cell lines showed genome damage using the DNA damage marker -ɣH2AX. But the responses to the virus invasion varied in different

cells. DNA damage marker-ɣH2AX was detected in all infected cells, but not before 4 hours, such as in H1299 cells. In these cells the ɣH2AX levels were similar for 8-16 hours after infection, in Vero cells - increased approximately 8-fold 4-8 hours after infection. Significant induction of ɣH2AX in HeLa and H1299 cells resulted from Myc-Nsp13 overexpression. But, all IBV-infected cells stopped cycling in the S-phase [44].

Genetic damages of immune cells were associated with the expression of seven genes (IFNAR2, TYK2, CCR2, CCR3, CXCR6, MAT2B, OAS3) during severe courses of COVID-19. A study of severe, moderate and mild COVID-19 identified 19 independent loci that were associated with disease severity [22] in another report with 13 significant loci associated with some aspect of SARS-CoV-2 infection [23]. It would be interesting to investigate these loci under the influence of antiviral drugs and to analyze whether it is possible to change the severity of the disease in this way.

ACE2 expression has been positively related to patients' age [4,18,35,36], and its increase has been correlated with telomere shortening or dysfunction and has also been observed in response to DNA damage [21]. Thus, the increased susceptibility of elderly people to COVID-19 may be related to telomere dysfunction occurring during the ageing process. When telomeres become critically short, they are perceived as double-stranded DNA breaks. In addition, telomeres tend to accumulate DNA damage regardless of their length, as evidenced by markers of DNA damage activation [36].

Telomeres are known to play a role in maintaining genome stability by protecting the ends of chromosomes (Callen E, Surralles J, 2004; De Lange T, 2005). Shelterin is a specific protein complex consisting of six subunits (TRF1, TRF2, POT1, TPP1, TIN2 and Rap1) has been shown to protect telomers. These proteins bind to telomere sequences to prevent double-strand breaks at the ends of chromosomes (De Lange T, 2005). Three of them (TRF1, TRF2 and POT1) directly recognize TTAGGG repeats in telomeres. Moreover, TRF2 is one of the most important proteins of the shelterin, providing telomere protection as it maintains telomere length and genome integrity. Three other shelterin proteins, TIN2, TPP1 and Rap1, interact with the three previous proteins, thereby forming a complex to distinguish between telomeres and DNA damage sites (De Lange T, 2005). Telomere shortening is caused by the loss of the shelterin components or its depletion (Oganesian L, Karlseder J, 2009).

SARS-CoV-2 infection has been shown to reduce the expression of telomere repeat binding factor 2 (TRF2) of the shelterin complex whose gene is located on chromosome 16 (16q22.1) and leads to a decrease in telomere length in SARS-CoV-2-infected cells (Vero E6). It has been shown that SARS-CoV-2 can trigger mechanisms leading to DNA damage in these cells (Victor J, Deutsch J, Whitaker A, Lamkin EN., *et al*. 2021). 48 hours after infection, SARS-CoV-2 activates the ATR-DDR pathway in Vero E6 virus cells, allowing the virus replication cycle to complete. In SARS-CoV-2-infected cells, in addition to telomere shortening, TRF2 expression was suppressed and the level of phosphorylated γH2AX was increased. By SARS-CoV-2 infection, telomere and host cell genome instability occurs due to ATR activation [29]. Telomere fusion and/or telomere shortening is due to TRF2 suppression. However, it is unknown how SARS-CoV-2 could modulate TRF2 expression and destabilize telomere length (Victor J, Deutsch J, Whitaker A, Lamkin EN., *et al*. 2021).

Of particular interest are the so-called topologically associated domains (TADs) [26,27], representing "large genomic regions containing multiple long-range regulatory sequences that coordinately control one or more target genes" (Miele A, Dekker J, 2008). Domains of chromatin with a high frequency of interaction and relatively isolated from neighboring regions form these TADs [26], which are structures defined by an increased probability of internal physical interactions [27]. It has been proposed how TADs are formed, involving two types of chromatin: type A and type B (Oganesian L, Karlseder J, 2009, Omoush SA, Alzyoud JAM (2022). While type A is highly enriched for open chromatin, type B is enriched for closed chromatin (Lieberman-Aiden E, van Berkum NL, Williams L., *et al*. 2009; Kalhor R, Tjong H, Jayathilaka N., *et al*. 2011; Sexton T, Yaffe E, Kenigsberg E., *et al*. 2012). It has been suggested that the TAD may replicate as a stable unit and play a role in maintaining the cellular genome phase and the premitotic phase G2. It is assumed that the mechanics of the formation of loops of the chromatin-Cohesin complex on the distal elements form the boundaries of the TAD. Under stress in the cell, stress replication occurs, which leads to more fragile genomic regions, which can be the beginning of chromosomal rearrangements and genomic instability (Kinjal Majumder, Abigail J Morales, 2021).

In the absence of any viral infection in intact cells, the increase in the chromatin environment is due to intrachromosomal contacts between pairs of chromosomes. But viruses can increase the available chromatin by modulating cellular TADs. Viruses can then use this chromatin environment for their replication centers, while simultaneously evading the host's antiviral defense factors. Here, for example, is some information on the increase in the chromatin environment in an intact cell. That happened by interaction of gene-rich chromosomes (chromosomes 16, 17, 19, 20, 21, and 22) (Lieberman-Aiden E, van Berkum NL, Williams L., *et al*. 2009; Kinjal Majumder, Abigail J Morales (2021). However, in the case of viral infection, these natural intrachromosomal interactions (which increase this chromatin environment) can have detrimental consequences for the host. This is important information about the presence of chromatin surroundings in the nucleus as some evidence suggests that the cell nucleus plays a role in coronavirus (infectious bronchitis virus) replication. Inhibition of nuclear export reduced IBV replication. In cells without nucleus (enucleated cells), viral replication was shown to be greatly reduced (Chen, M., Y. Ma, and W. Chang, 2022). These authors provide interesting data from other researchers stating that "avian IBV, a gamma-coronavirus, cannot replicate in enucleated cells. The murine hepatitis virus, a beta-coronavirus, can replicate in enucleated cells, but viral production is greatly decreased (down to 0.6 - 15% of control nucleated cells, dependent on the virus strains)" (Wilhelmsen KC, Leibowitz JL, Bond CW, Robb JA,1981). Replication of SARS-CoV-2 in enucleated cells has not been tested (Chen, M., Y. Ma, and W. Chang, 2022).

The suppression of the production of functional B and T cells leads to immunodeficiency. This is due to a repair defect with a non-homologous end joining (NHEJ), which in turn occurs due to the loss of key cellular DNA repair proteins, such as ATM, DNA-PKcs, 53 BP1 and others (Bednarski JJ, Sleckman BP, 2019; Bednarski JJ, Sleckman BP, 2012; Difilippantonio S, Gapud E, Wong N., *et al*. 2008). It has been hypothesized that only the full-length SARS-CoV-2 S protein strongly inhibited NHEJ and HR repair and directly affected DNA repair in the nucleus, although this protein does not alter host cell morphology. In addition to the discovery that the adhesion protein inhibits DNA repair, SARS-CoV-2 S proteins have been shown to be not only enriched in cell membrane fractions but also abundantly present in chromatin-associated nuclear cell fractions (Jiang H, Mei YF, 2021).

The immune response of B- and T-cells is based on V(D) J recombination, which requires DNA repair, especially NHEJ (Bednarski JJ, Sleckman BP, 2019). It has been suggested that older people suffer from a more severe form of COVID-19 because the S protein SARS-CoV-2 strongly suppresses the DNA repair system (Huang Y, Yang C, Xu XF., *et al*. 2020). Some authors suggest that DNA damage and mitotic errors, which result in aneuploidy and micronuclei, contribute significantly to the age- and sex-dependent aggravation of COVID-19 and cause cytokine storms [14].

Why can coronavirus cause such mutagenic effects? This is an important question. Perhaps we can partially find one answer in an article by Netherton, C.L. and T. Wileman (2011). Particularly their description of the formation of so-called "viral factories", or "double membrane vesicles" (DMVs), "viroplasm" that is generated in coronavirus-infected animal cells, is interesting. During coronavirus infection, networks of DMVs are formed in the cell, consisting of densely packed vesicles whose membranes are formed from the endoplasmic reticulum [25]. Coronavirus replication was observed to decrease (e.g. 1000-fold in murine hepatitis virus) with a decrease in the number of DMVs. DMV vesicles (Delorey TM, Ziegler CGK, Heimberg G., *et al*. 2022) are labelled with the autophagy marker (LC3), confirming autophagy activation by coronavirus (Mari M, Tooze SA, Reggiori F, 2011; Lieber MR, 2010). However, not all DMVs are autophagosomes (Zou L, Elledge SJ, 2003).

Most importantly, it has been shown that "Virus assembly and replication can also occur in "virus factories" close to the cell microtubule organizing center (MTOC)" [25]. Aggresome*s* (dynamic clusters of misfolded proteins in the cell, which form under stress conditions when the cell's protein degradation system is suppressed, and accompanied by redistribution of the intermediate filament protein vimentin) and 'virus factories' share many features and perhaps coronaviruses can also provoke of the aggresomes formation [25]. Dynein (a microtubule motor protein) plays a role in the delivery of many viruses to MTOCs. The dynein and kinesin motor is not limited to a transport role; it also plays an important role in the intracellular pathogenesis of viruses (Dodding MP, Way M, 2011).

Suggested that the suppression of innate immune responses is due to the storage of viral RNA in the spherules. We can be assumed

that the formation of "virus factories" or "viroplasmas" during coronavirus reproduction near MTOCs can negatively influence their function and may be one of the mechanisms of how the virus influences on cell division.

SARS-CoV-2 co-infection with other viruses

It is important to note that co-infection of a cell or human with SARS-CoV-2 and other viruses (e.g. RNA viruses) may have even more pronounced effects on the genetic apparatus of the host cell than mono-infection. Consider the following situations: meta-analysis has shown that the percentage of SARS-CoV-2 co-infections is as high as 10%. Co-infections were usually caused by influenza virus, respiratory syncytial virus, rhinovirus/enterovirus (Nowak MD, Sordillo EM, Gitman MR., *et al*. 2020; Musuuza JS, Watson L, Parmasad V., *et al*. 2021) and - less frequently - by other CoVs, adenovirus, parainfluenza virus or human metapneumovirus (Nowak MD, Sordillo EM, Gitman MR., *et al*. 2020; Lv Z, Cheng S, Le J., *et al*. 2020). In another study, SARS-CoV-2 coinfection was as high as 20%. The percentage of SARS-CoV-2 coinfection with rhinovirus/enterovirus ranged from 0.73% (Nowak MD, Sordillo EM, Gitman MR., *et al*. 2020) up to 6.9% (Kim D, Quinn J, Pinsky B., *et al*. 2020).

The current literature lacks convincing data on the molecular mechanisms underlying the interaction between SARS-CoV-2 and related pathogens (Omoush SA, Alzyoud JAM, 2022). Co-infection experiments using influenza A virus (IAV) and pseudo typed or true SARS-CoV-2 virus showed that pre-infection with IAV significantly increased the infectivity of SARS-CoV-2 in a wide range of cell types. Increased SARS-CoV-2 viral load and more severe lung damage were observed in mice co-infected with IAV (Bai L, Zhao Y, Dong J., *et al*. 2021). This study shows that IAV can exacerbate SARS-CoV-2 infection. Patients with simultaneous infection with dengue virus and SARS-CoV-2 had a high risk of mortality and critical illness (Tsheten T, Clements ACA, Gray DJ., *et al*. 2021). COVID-19 patients co-infected with viral pathogens had longer hospital stays compared to patients co-infected with atypical bacterial pathogens (Ma L, Wang W, Le Grange JM, 2020).

SARS-CoV has previously been shown to dysregulate the expression of genes related to immune function in monocytes. On this basis, it can be assumed that SARS-CoV-2 may have the same effect. Furthermore, SARS-CoV-2 differentially regulates the genes responsible for Toll-like receptor (TLR) signaling and other inflammatory pathways, which creates a suitable pro-inflammatory environment for bacterial co-infection (Manna S, Baindara P, Mandal SM, 2020).

Consider the action of other viruses accompanying SARS-CoV-2 as a co-infection. Although we focused on coronaviruses, it is very important to understand the possible general aspects of the action of other RNA viruses (on genetic structures). Especially for those viruses that have co-infected with SARS-CoV-2 as a co-infection.

Let us focus on how viruses identified as co-infected with SARS-CoV-2 caused damage in the genetic structures of cells in the case of mono-infection caused by them, influenza A virus infection induces DNA damage both *in vitro* and *in vivo* (Li N, Parrish M, Chan TK, Yin L., *et al*. 2015). Influenza A subtype H3N2 virus causes DNA damage in white blood cells as early as 2 hours after infection as confirmed by Comet assay (Vijaya Lakshmi AN, Ramana MV, Vijayashree B.., *et al*. 1999). DNA damage peaked after 24 h, although significant cell death was not observed until 96 h. Possibly, infected cells in the presence of deleterious mutations can continue to proliferate. A subsequent study found that the same influenza virus subtype causes extensive chromatin condensation and DNA fragmentation, consistent with apoptotic cell death (Khanna M, Ray A, Rawall S., *et al*. 2010). Another major subtype of influenza A virus, H1N1, has been shown to cause DNA strand breaks in both epithelial cells and immune cells, detected by the appearance of γH2AX foci (Li N, Parrish M, Chan TK, Yin L., *et al*. 2015). Increased levels of oxidative stress induced by viral infection correlated with DNA damage, which persisted even after the virus had disappeared. The host inflammatory response appears to be at least partly responsible for the DNA damage caused by influenza A virus infection, which subsequently plays a role in the localized tissue damage that characterizes viral disease. It remains unclear which specific influenza A virus proteins are responsible for the induction of DNA damage and whether the repair pathways of the virus are disrupted [33].

Human respiratory syncytial virus (HRSV), one of the viruses frequently co-infected with SARS-CoV-2, causes the expression of DNA damage markers (such as P-TP53, P-ATM, CDKN1A and γH2AFX) as well as proliferation arrest. During infection with

HRSV, two markers (γH2AFX and TP53BP1) were found at DNA double-strand breaks (DSBs). Even long after (up to 30 days) HRSV disappeared, DNA damage and cellular senescence (expression of γH2AFX and CDKN2A) were detected in the respiratory epithelium of infected mice. Thus, HRSV triggers a DNA damage-mediated cellular senescence programme (Martinez I, Garcia-Carpizo V, Guijarro T., *et al*. 2016).

Rhinoviruses induce apoptosis and necroptosis in epithelial cells in the later stages of infection (Lotzerich M, Roulin PS, Boucke K., *et al*. 2018). The process of apoptosis proceeds as follows: the caspase-independent proteins of rhinoviruses (AIF and endonuclease G) are transported to the nucleus, where they start chromatin condensation followed by DNA fragmentation. Completes of the process of chromatin condensation and DNA fragmentation the CAD protein that moves from the mitochondria to the nucleus (Kerr SL, Mathew C, Ghildyal R, 2021).

There is a hypothesis that the localization of protein VII in the host chromatin during adenovirus infection inhibits DDR signaling and affects DNA damage (Avgousti DC, Della Fera AN, Otter CJ, Herrmann C., *et al*. 2017). Adenoviruses inhibit double strand break repair and are physically associated with the cellular DNA-dependent protein kinase [6] since the mechanisms of DNA damage induced by DNA viruses has been described by Kinjal Majumder, Abigail J Morales (2021), we do not focus on DNA viruses in the present review.

Recently, data have been presented on the effect of norovirus infection on DNA damage due to leakage of both mitochondrial (aberrant) and genomic DNA into the cytosol of cells (infected with murine norovirus) (Aminu S. Jahun FS, Yasmin Chaudhry., *et al*. 2021). The viral protein norovirus (VPg) leads to G0/G1 arrest, which is its conserved function (McSweeney A, Davies C, Ward VK, 2019) and G1/S arrest (Davies C, Ward VK, 2016).

Thus, we summarize here not only the effects of SARS-CoV-2 on the genetic apparatus of target cells, but also the effects of other viruses that can co-infect the susceptible organism and cause more deleterious effects on the heredity apparatus. Detailed studies of the interaction between SARS-CoV-2 and other viruses in the same cell, especially the impact on the cell genome in co-infections, are needed, so we raise these questions. Obviously, we do not present a complete list of viruses that can cause coinfection with SARS-CoV-2 and this area of research requires future research.

Recently, many additional target cells for SARS-CoV-2 have been identified outside the respiratory tract (e.g., in semen, retina, kidney, intestines, liver, and pancreas). The effects of SARS-CoV-2 on the genomes of these cells may also contribute to the pathogenesis of COVID-19 and potentially long-term sequelae of the virus.

Conclusion

SARS-CoV-2 adversely affects the genetic machinery of infected humans cells. Taking into account the discovery of more and more target cells for this virus, the consequences of viral infection can be more profound and dangerous for patients who survived than initially thought and help to explain the pathogenesis of «Long-COVID». Notably, SARS-CoV-2 infections are frequently accompanied by infections with other viruses. Combined action of many viruses in one target cell may have cumulative negative effects on DNA integrity and other nuclear structures and, as a consequence, cause disruption of cellular and tissue metabolism. These aspects should be considered when developing preventive and therapeutic approaches to fight coronavirus infection.

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Ethics Declaration

The manuscript does not involve any human participants or biological material, nor any animals.

Ethics Approval

This manuscript is a review (opinion) article. An approval by the ethics committee is not required since no experiments were performed.

Conflict of Interests

The author declares that she has no financial interests.

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Author Contributions

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Consent to Participate

This manuscript does not involve any research on human subjects.

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This manuscript does not publish.

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