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The effects of SARS-CoV-2 on susceptible human cells

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The biological consequences of viral infection result from biochemical, physiological, structural, morphological and genetic changes in infected cells. In productive infections, virus-induced biological changes in cells may be closely related to the efficiency of viral replication or to the recognition of these cells by the immune system. These changes are usually associated with cytocidal viruses, as in the case of the pandemic coronavirus SARS-CoV-2, which causes COVID-19. Many of these changes are required for effective viral replication. The physiological state of living cells has a significant impact on the outcome of viral infection, as the host cell provides the synthetic machinery, key regulatory molecules and precursors for newly synthesised viral proteins and nucleic acids. This review focuses on novel target cell types for SARS-CoV-2 exposure outside the respiratory tract. Findings and examples are collected that provide information on virus-cell interactions. The identification of unusual target cells for SARS-CoV-2 may help to explain the diverse symptoms in COVID-19 patients and the long-lasting effects after infection. In particular, the discovery of previously undescribed target cells for SARS-CoV-2 action needs to be considered to improve treatment of patients and prevention of infection.

KEYWORDS

SARS-CoV-2, susceptible human cells, olfactory sensory neurons (OSNs), influence, virus-cell interactions

Introduction

From 2019, we will face a new emerging pathogen that is perfectly adapted to a new host (humans). We know that COVID-19 has been declared a pandemic by the World Health Organisation (WHO) since March 2020. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that caused this pandemic is rapidly evolving, finding possible new targets, ecological niches and new mechanisms of interaction with host cells. Since the discovery of SARS-CoV-2, several mechanisms of COVID-19 pathogenesis and interaction with its target cells have been described, as well as several mechanisms of immune evasion by the virus. The pathophysiology of SARS-CoV-2 infection is very similar to that of SARS-CoV. The severity of disease in patients is determined not only by

Abbreviations: CNS, central nervous system; OSNs, olfactory sensory neurons; PASC, post-acute sequelae of COVID-19; h.p.i., hours post infection.

the virus itself, but also by the (immune) status and the host cell/body response. The severity of the infection is also known to be determined by the age, sex, diet and co-morbidities (diabetes, cardiovascular disease, cancer, immunodeficiency) of the infected individual (Aman and Masood, 2020; Li and Li, 2020; Scully et al., 2020; Xie et al., 2020; Cenko et al., 2021; Sen et al., 2021; Kim et al., 2022). Several modes of transmission have been described for SARS-CoV-2, including aerosol transmission, surface contamination and the faecal-oral route, leading to severe influenza-like symptoms, including fever, cough and dyspnoea (Chen et al., 2020a; Harrison et al., 2020; Zhou et al., 2021). Transmission appears to be affected by temperature, humidity, precipitation, air currents, pH and ambient radiation (Ma et al., 2021; Nottmeyer et al., 2022). SARS-CoV-2 is highly contagious and has broad tissue tropism. Important questions remain regarding its pathogenesis at the cellular level (Harrison et al., 2020; Bridges et al., 2022). Many researchers focus on the known facts of SARS-CoV entry [9] into the host via the respiratory tract (Hui et al., 2020), into human lung tissue (Chu et al., 2020), into alveolar epithelial cells, vascular endothelial cells and alveolar macrophages, which are among the first to be entered by the virus (Bridges et al., 2022). They concluded that these cells are likely to be the "zero point" for early infection and subsequent replication because of their expression of ACE2 (Bilinska et al., 2020; Djomkam et al., 2020; Hoffmann et al., 2020). However, it turns out that there are many other cells that are sensitive to the virus. COVID-19 is known to be a complex disease with clinical responses ranging from asymptomatic to severe with catastrophic respiratory failure and death. The broad tissue tropism of the virus can be confirmed by looking at other susceptible cell types as well as different animal cell lines (Ogando et al., 2020; Wang et al., 2021) as well as human cell lines (colon cancer cell lines CL-14 and CL-40, breast cancer cell line CAL-51), and CACO-2, CALU-3) (Pommerenke et al., 2021). ACE2 (angiotensin-converting enzyme 2) and TMPRSS2 (serine transmembrane protease 2) expression has been found to be indicative but insufficient for productive SARS-CoV-2 infection in human cell lines (Qi et al., 2020; Pommerenke et al., 2021), probably due in part to a shortened splice variant of ACE2 and variants of TMPRSS2. Several organs and cell types have now been reported to be infected with SARS-CoV-2, even in those with no or low baseline ACE2 expression (Singh et al., 2020; Zou et al., 2020). Some therapies will need to be modified to contain SARS-CoV-2 once we understand how and which cells the virus enters and affects.

Susceptible human cells to SARS-CoV-2 outside the respiratory tract

One of the main problems with COVID-19 is the large number of patients requiring extended respiratory support due to acute respiratory distress syndrome (ARDS), as the lungs are the main, although not exclusive, target of the virus (Carcaterra and Caruso, 2021). We first started with the more studied target cells of SARS-CoV-2 replication. Like SARS-CoV, SARS-CoV-2 primarily targets airway epithelial cells, alveolar epithelial cells, vascular endothelial cells and macrophages in the lungs, all of which express ACE2, which the virus uses as an entry receptor (Hamming et al., 2004; Jia et al., 2005; Xu et al., 2020a).

The molecular mechanisms, pathogenic factors and target cell type(s) of SARS-CoV-2 infection are still poorly understood (Ahn et al., 2021; Carcaterra and Caruso, 2021). The upper airways are affected in early COVID-19, but the tropism of SARS-CoV-2 at the cellular level has not been fully defined (Ahn et al., 2021). Some researchers have found that the cellular tropism of SARS-CoV-2 is restricted to the ciliated epithelium of the nose compared with the squamous epithelium of the oral cavity (Ahn et al., 2021). Some researchers have suggested that the human upper respiratory tract, particularly the nasal cavity, may be the primary site of viral replication and transmission of SARS-CoV-2. There is a theory that type II alveolar epithelial cells are the primary targets of SARS-CoV-2 and that the clinical manifestations of the syndrome are a direct consequence of their involvement (Carcaterra and Caruso, 2021).

The nasal epithelium is covered by a thin layer of mucus with active cilia that ultimately traps and removes pathogens, including SARS-CoV-2, and particulate matter from the inhaled air. Although this epithelium serves as the first line of defence against lower respiratory tract infections, it may also be a target tissue for the proliferation of SARS-CoV-2 and other pathogens (Gengler et al., 2020; Lamers et al., 2020). Most importantly, accumulating evidence suggests that SARS-CoV-2 affects not only respiratory and lung epithelial cells, but also epithelial and non-epithelial cells in other organs that express ACE2 (Aiello and Moses, 2016; Gupta et al., 2020). When determining the cellular and tissue tropism of a virus, it is important to remember that the presence of viral mRNA in a cell does not necessarily imply productive viral replication in a given cell type. A cell that can be infected is susceptible but does not always ensure that the viral replication cycle is completed (i.e., is not necessarily permissive). Several authors have studied the pathogenesis of SARS-CoV-2 using different model systems, including 2- and 3-dimensional organoid cultures of bronchial or lung epithelial cells (Ahn et al., 2021; V'Kovski et al., 2021).

The results (Ahn et al., 2021) demonstrate that nasal multiciliated epithelial cells are the main target cells for SARS-CoV-2 infection and replication in the upper respiratory tract during the early stages of COVID-19. And then? What cell types does the virus target further outside the respiratory tract? Do all variants of the virus spread further to other cells or does it depend on the virus strain?

In February 2022, comparative studies (Hui et al., 2022) were published with different virus strains (Alpha (B.1.1.7), Beta

(B.1.351), Delta (B.1.617.2) and Omicron (B.1 .1.529) and their cellular tropism in *ex vivo* cultures of human bronchial and lung explants. These virus variants showed different rates of viral replication, but all showed similar cellular tropism. Omicron was found to replicate faster in bronchi than the others, but less efficiently in lung parenchyma. It has been observed that the Omicron variant penetrates cells in a different way compared to the other variants, that it is more cathepsin dependent than the others (Hui et al., 2022) and in an endosomal pathway independent of TMPRSS2. In primary human airway cells the Omicron variant replicated much more rapidly than Delta virus too. Also have been found that Omicron Spike bound better to mouse ACE2 than any previous virus variant that can leads to possibility it widespread (Peacock et al., 2022a). But, the Delta variant replicated faster than the Omicron variant in the VeroE6/TMPRSS2 and Calu3 cell lines (Zhao et al., 2022). However, in comparative studies on another cell culture, the epithelial cells of the human nasal passages (HAE), the Omicron and Delta variants showed an advantage for Omicron in early replication after 24 h. It showed about 100 times higher titres than the Delta variant. However, after 48 and 72 h, the Delta variant showed higher titres than Omicron (Peacock et al., 2022b). Other authors (Mautner et al., 2022) performed experiments with a fixed number of infectious units on three cell cultures: Vero E6, Caco-2 and Calu-3. They used five variants of SARS-CoV-2: Alpha/B.1.1.7, Beta/B.1.351, Gamma/P.1, Delta/B.1.617.2 and Omicron/B.1.1.529 as well as a non-VOC/B.1.1 strain. "While the ratios for Alpha, Beta, and Gamma were comparable, tenfold less infectious particles for the same genome copy number were obtained for Delta and Omicron, but tenfold more for the non-VOC strain, respectively. This is reflected in variations of the genome copy numbers obtained at the start of the infection experiments, as these were started with a fixed number of infectious units" (Mautner et al., 2022).

Despite the significant difference in individual kinetics in different cells between all the virus variants tested up to 96 h.p.i. all achieved the same number of virus RNA copies (Mautner et al., 2022). Now Omicron has become a leading version of the virus causing the COVID-19. Initially, Omicron had three sub-variants (e.g., BA.1, BA.2 and BA.3) (Islam et al., 2022). Omicron was first spotted in South Africa and Botswana in November 2021 (Callaway, 2021). The sub-variants BA.1 was predominant during the fourth wave of the pandemic in South Africa. However, variants BA.4 and BA.5 (categorized as VOC on 12 May 2022 and detected in a sample collected in South Africa in early 2022) are now predominant in Europe and the United States. Omicron's sub-variants BA.4 and BA.5 have similar spike proteins that are most similar to BA.2. These Omicron options have spike mutations at positions 69-70del, L452R and F486V (Islam et al., 2022). The subvariants of Omicron BA.4 and BA.5 allow them to infect more people more quickly. The spike mutation at position L452R is responsible for the increased transmissibility. The Delta variant carried this mutation. The Omicron BA.4 and BA.5 sub-variants can become more infectious because this mutation helps the virus to attach to the human cell. Another important mutation in the BA.4 and BA.5 sub-variants is F486V. This mutation occurs in the spike protein region near the attachment site to the human cell. This mutation may help the virus to be more infectious and to fool the human immune system. This is why these new variants have a greater capacity to infect immunized people than the earlier variants and forms of Omicron (Islam et al., 2022). Nine of the 15 mutations in the Omicron spike region enter the binding zone of the virus' main receptor, ACE2. These mutations in the RBD could potentially confer an evolutionary advantage by increasing ACE2-RBD viral binding or avoiding detection by neutralizing antibodies (Dejnirattisai et al., 2022; Chatterjee et al., 2023). Among hypotheses is one to explain why Omicron shows rapid replication in nasal cells is that, due to its large number of receptor binding domain (RBD) mutations, Omicron might use a different protein receptors those used by other coronaviruses (Peacock et al., 2022a).

In susceptible populations during a pandemic, the virus can spread mutations that alter pathogenicity, virulence and/or transmissibility. Recently, many cells other than nasal multi-ciliated epithelial cells, bronchial or pulmonary epithelial cells are known in which the virus can replicate, and for this reason we can also call these cells targets for the virus.

The more severe form of COVID-19 is known to be associated with older age, comorbidities and male gender. It turns out that SARS-CoV-2 affects more than just the respiratory tract. Other organ systems, such as the nervous system, may also be affected. The virus RNA has been found in autopsies on the brains of patients who have died of COVID-19. Sun et al. (Sun et al., 2020) reported that viral RNA was found in many organs in patients with COVID-19, as described by other authors (Alves et al., 2020; Brann et al., 2020; Zhang et al., 2020b; Gupta et al., 2020; Guterres et al., 2020; Han et al., 2020; Jin et al., 2020; Mao et al., 2020; Pan et al., 2020; Robbins-Juarez et al., 2020; He et al., 2021; Muller et al., 2021; Pandanaboyana et al., 2021; Perez-Lago et al., 2021; Bhavya et al., 2022; Jansen et al., 2022; Menuchin-Lasowski et al., 2022). The SARS-CoV-2 entry receptor (ACE2) is expressed in many extrapulmonary tissues. Therefore, direct tissue damage by the virus is likely in many organs (Zou et al., 2020; Beyerstedt et al., 2021). We therefore consider other susceptible to virus cells recently discovered.

SARS-CoV-2 and nervous cells

In COVID-19 patients reported different neurological symptoms, including headache, encephalitis, and altered mental status (Mao et al., 2020). Autopsy, animal studies and organoid models show that, like SARS-CoV, SARS-CoV-2 is able to reach and infect CNS cells, infect neurons and induce

neuroinflammation (Matschke et al., 2020; Song et al., 2021). Indeed, SARS-CoV-2 can be transported up and down neurons and neurons axons (Lima et al., 2020; Mao et al., 2020; Karuppan et al., 2021; Rangon et al., 2021). There is still debate about the haematogenous or transsynaptic spread of SARS-CoV-2, its spread across the blood-brain barrier, the effect of the hyperimmune response ("cytokine storm") and the possible persistence of the virus in some CNS resident cells. The severity of neurotropism and neurovirulence in patients with COVID-19 may depend on both viral and host factors and their interaction (Pennisi et al., 2020). One consistent clinical feature, which can appear before the onset of respiratory symptoms, is the disturbance in olfaction and gustation in patients with COVID-19 (Douaud et al., 2022), as for example, olfactory dysfunctions such as anosmia, hyposmia, reduction of smell. The main mechanism is associated with damage to the olfactory epithelium, predominantly affecting non-neuronal cells. However, neuronal cells can also be affected, exacerbating the condition of olfactory loss. It is interesting what is about anosmia, loss of the ability to smell, a well-known feature of many cases of SARS-CoV-2. There is evidence of inhibition of olfactory receptor function, as well as of key components of the relevant signaling pathways (Zazhytska et al., 2021; Zazhytska et al., 2022). In studying the symptom of anosmia in COVID-19 and trying to understand the mechanisms of this phenomenon, interesting findings have emerged. Anosmia is interesting in that it has become a hallmark and is often (but not always) seen as a major (key) symptom of COVID-19 in many cases of the disease, even in asymptomatic patients. However, the molecular mechanism of this phenomenon remains unclear. In particular, the mechanism by which olfactory sensory neurons function in anosmia. SARS-CoV-2 infection suppresses olfactory receptors (responsible for detecting odours and transmitting this information to the brain) in the olfactory epithelium (Las Casas Lima et al., 2022; Peacock et al., 2022b). Olfactory sensory neurons (OSNs) do not express ACE2 and TMPRSS2, receptors required for virus entry into the host cell (Bilinska et al., 2020; Brann et al., 2020). Recent studies of the respiratory epithelium in the human nasal cavity have not detected clear ACE2 signaling (Ruiz Garcia et al., 2019; Deprez et al., 2020). Thus, the virus may infect olfactory neurons in different ways (Brann et al., 2020), for example, using different cell receptors, or anosmia occurs due to an autonomous extracellular state. According to some reports, it is in the sustentacular cell layer that both host receptors for SARS-CoV-2 are expressed and are required for cellular invasion. It is thought that SARS-CoV-2 first accumulates in the supporting cells and, by interfering with their metabolism, mechanistically affects olfactory receptor neuronal function. However, whether the virus can be transmitted from sustentacular cells to olfactory receptor neurons remains an open question requiring further research (Butowt et al., 2021). The tropism of Delta and Omicron strains in the nasal cavity has not been clarified. SARS-CoV-2 WA1 or Delta affects a subset of olfactory neurons in addition to the primary supporting target cells. The Delta variant has a greater capacity for cell invasion into the submucosa. The Omicron variant is retained longer in the sinonasal epithelium. In younger hosts, infection of olfactory WA1 neurons and subsequent transport through the olfactory bulbs into the axon is more pronounced (Chen et al., 2022). Interesting was that some authors found no nucleocapsid protein in the axon bundles of olfactory sensory neurons (Park et al., 2022), suggesting that SARS-CoV-2 may enter the CNS via the olfactory system (Varatharaj et al., 2020; Chen et al., 2022; Las Casas Lima et al., 2022).

Some RNA viruses cause genome instability and induction of DNA damage response (DDR), and also the appearance of micronuclei (MN). SARS-CoV-2 can trigger mechanisms leading to DNA damage in Vero cells (Victor et al., 2021) and other susceptible cells and models (Klestova, 2023). The researchers wondered whether SARS-CoV-2 infection affects the nuclear structure of the OSN. They found a decrease in genomic compartmentalization during viral infection. Experiments on hamsters showed that already 3 days after infection a strong decrease in the number of predicted genomic compartments in OSN nuclei was observed compared to the control. An abrupt change and reorganization of the nuclear architecture caused by SARS-CoV-2 infection and exposure to various genes, including those required for odor detection, was shown. It is suggested that the initiation of cytokine induction in virus-infected cells leads to dramatic changes in the reorganization of the OSN nuclear structure and dissociation of genomic compartments. The nuclear reorganization of OSNs removes their ability to recognize odors and transmit this information to the brain (Las Casas Lima et al., 2022). A likely explanation for the reduction in olfactory receptor (OR) transcription is the reorganisation of nuclear architecture observed in the OSN lineage, disrupting multi-chromosomal compartments that regulate OR expression in humans and hamsters. Have uncovered a novel molecular mechanism by which a virus with highly selective tropism can induce persistent transcriptional changes in cells that evade it, contributing to the severity of COVID-19 (Zazhytska et al., 2021). It has been suggested that this may be an attempt by the virus to circumvent the immune response, as mammalian cells use intrachromosomal contacts to activate antiviral programs (Apostolou and Thanos, 2008).

Chen et al. (Chen et al., 2022) demonstrated "a transition in tropism from olfactory to respiratory epithelium as the virus evolved. Analyzing of each virus variants revealed that SARS-CoV-2 WA1 or Delta infects a proportion of olfactory neurons in addition to the primary target sustentacular cells. The Delta variant possesses broader cellular invasion capacity into the submucosa, while Omicron displays longer retention in the sinonasal epithelium. The olfactory neuronal infection by WA1 and the subsequent olfactory bulb transport via axon is more pronounced in younger hosts. In addition, the observed

viral clearance delay and phagocytic dysfunction in aged olfactory mucosa is accompanied by a decline of phagocytosis related genes. Furthermore, robust basal stem cell activation contributes to neuroepithelial regeneration and restores ACE2 expression post-infection".

In nasal turbinates Omicron induced higher viral loads than in the lung (McMahan et al., 2022) and proposed that Omicron is less specialized in cell tropism, so it infects more types of cells (Peacock et al., 2022a).

Thus, a molecular explanation is shown for the SARS-CoV-2-induced anosmia by which this virus can alter the identity and function of host cells devoid of receptors for viral entry. Adult CNS neurons also form long-range cis- and trans-genomic compartments, an adaptive process that may eventually cause long-term changes in the nuclear architecture of the brain, explaining the cognitive and neurological impairments associated with SARS-CoV-2 infection (Las Casas Lima et al., 2022; Peacock et al., 2022b).

Thus, a likely explanation for the decrease in olfactory receptor transcription is the striking reorganization of the host cell nuclear architecture in which the intrachromosomal compartments that regulate olfactory receptor expression in both humans and experimental hamsters are destroyed. An entirely new molecular mechanism has been shown by which a virus with very selective tropism can induce persistent transcriptional changes in cells that determine disease severity (Las Casas Lima et al., 2022; Peacock et al., 2022a).

SARS-CoV-2 and brain tissues

The interactions between SARS-CoV-2 and the host may result in a wide range of different pathways being affected by this virus. Continuing the topic of the effect of SARS-CoV-2 on the nervous system, it has been shown that the virus may be involved in pathogenesis (Nazari et al., 2021) by initiating/stimulating chromosomal instability of neurons (Pennisi et al., 2020; Iourov and Vorsanova, 2022). About 88% (78/88) of patients with COVID-19 with a severe course of the disease were found to have neurological manifestations, including acute cerebral circulation disorder and impaired consciousness (Zou et al., 2020). There is still a lack of research into the mechanisms involved in the pathogenesis of viral infection of the brain cells. In the brain, both in neurons and glia, SARS-CoV-2 receptor ACE2 is also expressed. And in the olfactory epithelium presence two host receptors, ACE2 and TMPRSS2, in some cell types that expressed. They facilitate SARS-CoV-2 binding, replication, and accumulation (Butowt and Bilinska, 2020; de Erausquin et al., 2021). In post-mortem brain tissue, ACE2 was found to be expressed in the vasculature of the frontal cortex, and viral C-spike proteins (spikes) caused damage to the blood-brain barrier (Buzhdygan et al., 2020; de Erausquin et al., 2021). For the first time, a direct effect of the SARS-CoV-2 spike protein on brain endothelial cells has been demonstrated. This may explain the neurological effects seen in patients with COVID-19 (Buzhdygan et al., 2020). A feature of the primary encephalopathy in patients with COVID-19 may be delirium due to the direct intracerebral invasion of the virus (Paniz-Mondolfi et al., 2020). Some authors consider that the secondary encephalopathy may be associated with neuroinflammatory response to SARS-Cov-2 immune-mediated systemic response or other factors (Mehta et al., 2020; Reichard et al., 2020).

Brain aging is known to be associated with chromosome/genome instability (Heng and Heng, 2021). COVID-19 has been shown to be associated with neurodegeneration (including Alzheimer's disease) due not only to advanced age of some elderly patients, but also to chromosome/genome instability due to coronavirus infection (Alves et al., 2020). In this case, chromosomal instability is superimposed on genomic abnormalities of brain cells associated with age-related chromosomal instabilities, leading to a complex of brain diseases (Xu et al., 2020b; Iourov and Vorsanova, 2022). Some authors confirmed that the long-term effects of SARS-CoV-2 infection may contribute to the development of Alzheimer's disease or other forms of dementia over time (de Erausquin et al., 2021; Douaud et al., 2022).

SARS-CoV-2 and retinal cells

The neural retina of the eye is known to contain several layers of nerve cells. They are interconnected by synapses and covered by an outer layer of pigment epithelial cells. The main light-sensitive cells in the retina are the photoreceptor cells, which come in two types: rods and cones. The third type of light-sensitive cells are the light-sensitive ganglion cells. This layer maintains circadian rhythms and reflex responses such as the pupillary light reflex.

New evidence is emerging that SARS-CoV-2 can also penetrate the retina. However, it is unclear which retinal structures are infected by the virus and whether the retinal abnormalities found in patients with COVID-19 are a direct or indirect result of retinal infection (Bertoli et al., 2020; Leung et al., 2022; Menuchin-Lasowski et al., 2022). Bertoli et al. shown that SARS-CoV-2 RNA has been found in tears of the infected patients, and reports suggest that the ocular surface could serve as a portal of entry and a reservoir for viral transmission. In a study by some authors (Menuchin-Lasowski et al., 2022) it was found that SARS-CoV-2 does infect retinal cells, especially two cell types: retinal ganglion cells as well as light-sensitive cells. The type of cells in the eye in which the N-protein of the virus has been most frequently detected are retinal ganglion cells. Located in the inner cell layer of the retina retinal ganglion cells transmit the signals from the retina to the brain via the optic nerve. Consequently, SARS-CoV-2 infection can have direct pathological effects on the retinal ganglion cells. Long-term symptoms of COVID-19 may therefore include degenerative retinal disease (Brantl et al., 2021; Firoz and Talwar, 2022).

SARS-CoV-2 and kidney and cardiac cells

Interesting studies formed the basis of the published atlas of tissues and their damage under the influence of SARS-CoV-2 and cellular targets (Delorey et al., 2021) but many target cells of virus in this atlas were not taken into account. This may be because information about new targets for the virus came later. Damage to heart tissue by the virus may be the main cause of heart disease in COVID-19 (Chung et al., 2021; Castiello et al., 2022; Yang et al., 2022). A common extrapulmonary manifestation of COVID-19 with potential chronic consequences is acute cardiac injury (Chung et al., 2021). A decrease in the proportion of cardiomyocytes and pericytes and an increase in vascular endothelial cells and other disturbances in tissues were observed by SARS-CoV-2 infection. Myocardial damage caused by SARS-CoV-2 is associated with disease severity and mortality. The pathogenetic mechanisms of this cardiomyocyte damage are not fully understood (Yang et al., 2022). Myocardial damage has been observed in patients with COVID-19, which can occur for a variety of reasons, including reduced oxygen levels, microthrombus formation, and direct damage to cardiomyocytes from viral infection (Fox et al., 2020). The effects of COVID-19 on cardiac contractility can be long-lasting and lead to heart failure. *In vitro*, damage to cardiomyocytes during viral infection has been demonstrated by the release of troponin into the culture medium and almost complete loss of coordination and inhibition of contraction (Siddiq et al., 2022). This is accompanied by a certain level of interleukins. However, interleukins do not increase the number of infected cells. Cardiac hypertrophy can also occur in response to the appearance of pro-inflammatory cytokines (IL-6 and IL-1β), which may be necessary to maintain cardiac homeostasis (Shimizu and Minamino, 2016; Liu et al., 2020). Human induced pluripotent stem cell-derived cardiomyocytes were infected with two strains of SARS-CoV-2 and showed that the virus infects cardiomyocytes *in vitro* in an ACE2- and cathepsin-dependent manner (Bojkova et al., 2020).

Deregulation of genes in cardiomyocytes, pericytes and fibroblasts was observed too. Oxidative stress in pericytes led to apoptosis, cell adhesion and immunopathology in cardiomyocytes, which was also observed during fibroblast differentiation. Delorey et all (Delorey et al., 2021). however pointed out that no viral RNA was found in the heart, liver and kidneys of patients with COVID-19, but changes were observed in the cells there.

However, many researchers have been found of SARS-CoV-2 in the kidney as in other organs (Silver et al., 2021; Jansen et al., 2022). As in lung macrophages, as in kidney, and adrenal stromal cells has been detected susceptible to SARS-CoV-2. Kidney damage is common and can range from mild proteinuria to progressive acute kidney injury (AKI) (both direct and indirect injury), leading to high mortality in patients with COVID-19 (Jin et al., 2020; Soleimani, 2020; He et al., 2022), in a manner which may contribute to PASC symptoms. Huang et al. (2021) found that even 6 months after acute COVID-19 infection, 35% of patients had a reduced estimated glomerular filtration rate (eGFR) (Huang et al., 2021). SARS-CoV-2 has been detected in both urine and the kidneys, where it is thought to cause damage to the proximal tubule cells and podocytes (Bronimann et al., 2020; Remmelink et al., 2020; Werion et al., 2020), causing acute renal damage (Chen et al., 2020b), leading to the release of the virus in the urine (Sun et al., 2020). A possible viral invasion mechanism was considered, involving the expression of ACE2, TMPRSS2 and furin, which are required for the virus to enter cells (Zhou et al., 2020). It has been showed that "ACE2 and TMPRSS2 overlap and are expressed in proximal convoluted tubular cells, proximal straight tubular cells and podocytes" (He et al., 2020).

Later, in 2022, a review on mechanisms of SARS-CoV-2 infection-induced kidney injury was published (He et al., 2022). This authors concluded that "several factors influence COVID-19-induced renal injury, including direct renal injury mediated by the combination of the virus and ACE2, indirect, dysregulation of the immune response, cytokine storm caused by SARS-CoV-2 infection, organ interactions, hypercoagulable state and endothelial dysfunction."

Thus, to develop new prevention and treatment options for COVID-19-induced AKI, further research is needed.

SARS-CoV-2 and gastrointestinal cells

The gastrointestinal (GI) tract represents an important aspect of human infection with SARS-CoV-2 (Zhang et al., 2020b; Han et al., 2020; Jin et al., 2020; Pan et al., 2020; Pegoraro et al., 2022). Patients with COVID-19 show a wide range of gastrointestinal symptoms, including anorexia, nausea, vomiting, abdominal pain and abnormal liver function. The virus itself may cause direct damage to the intestinal mucosa (Jin et al., 2020).

In addition, there have been reports of adverse effects of the virus on the liver, with significant changes in liver function tests, and when the liver is involved in the infection, the risk of death of patients increases (Zhang et al., 2020a; Lee et al., 2020; Lei et al., 2020; Pan et al., 2020; Richardson et al., 2020). Especially through an increase in the AST enzyme, which is associated with an increased risk of mortality (Lei et al., 2020).

The pancreas may also be a target organ for SARS-CoV (Hamming et al., 2004). It has been suggested that β-cell infection may contribute to metabolic dysregulation in infected patients. People with even a mild form of COVID-19 have a higher risk of developing diabetes a few months after infection than those who have never had the disease (Huang et al., 2021; Wander et al., 2022). SARS-CoV-2 disrupts glucose homeostasis; therefore, the virus can induce diabetes induced

SARS-CoV-2 due to β-cell disruption, which has been confirmed *in vivo* and *in vivo* on infected human pancreatic exocrine and endocrine cells (Hayden, 2020; Muniangi-Muhitu et al., 2020; Millette et al., 2021). MicroRNAs (miRNAs) play an important role in regulation of cellular gene expression. Host miRNAs in cells infected with SARS-CoV-2 can target native gene transcripts as well as viral genomic and sub genomic RNAs. MiRNAs primarily target the 3′UTR and 5′UTR genomes of viral RNA. During viral infection, host cell miRNAs may target the viral genome rather than the host mRNA. This leads to competition for microRNA regulation between host cell mRNAs and copies of the viral genome in the cell. This differential targeting of miRNAs can lead to the dysregulation of host cell genes as proved by the dysregulation of microRNA function in SARS-CoV-2-infected pancreatic cells from diabetic patients (Bhavya et al., 2022; Taylor et al., 2023).

SARS-CoV-2 and heredity apparatus

So far, we have given examples of the effects of SARS-CoV-2 on different human somatic cells of both sexes of patients or models, but what happens in human cells depending on gender, or better said, in cells with different karyotypes?

Males are known to be more susceptible to SARS-CoV-2 regardless of age. Genomic analysis has shown that there are about 800 genes on the X chromosome that code for protein products. The hACT2 gene is also located on this chromosome. Males are hemizygous for the ACE2 gene because males have one X chromosome and this gene is not represented by a second allele. Both ACE2 and TMPRSS2 are known to be key for SARS-CoV-2 entry into the cell (Wei et al., 2004; Delaneau et al., 2008). TMPRSS2 expression regulates androgen/estrogen stimulation. There are conflicting data on ACE2 expression levels in men and women. For most X-chromosome genes (including ACE2), double allelic dosage in females is balanced by epigenetic silencing of one X chromosome in early development. However, the inactivation of one X chromosome is incomplete. Some of the genes remain active, and this varies from person to person. The ACE2 gene is one of the genes that avoids inactivation on the X chromosome. Female carriers of this abnormal gene (if presents mutation in this gene) show a normal phenotype due to a second normal and functional copy of the hACT2 gene (Tsiambas et al., 2020). However, some scientists still consider it unlikely that there are differences between males and females in terms of the effects of the ACE2 and TMPRSS2 genes (Asselta et al., 2020).

Thus, it can be assumed that negative pathological processes can occur in any human tissue/cell during infection with SARS-CoV-2, and the virus can induce pathological changes in many host cell types in addition to the immunopathological response.

These results confirm that we will find new and newly susceptible cells for SARS-Cov-2 aggression by further investigation.

SARS-CoV-2 and spermatogenesis

It has been suggested that COVID-19 worsens semen quality in men depending on the severity of the disease. SARS-CoV-2 virus was detected in semen by PCR in 15.8% of patients (He et al., 2021). Semen analysis time was 2.5–7 days after infection. Semen quality was found to be lower in moderate infection than in mild infection or compared to uninfected controls. Viral particles were detected in testicular samples. SARS-CoV-2 has been shown to disrupt spermatogenesis, damaging chromatin and cell DNA, resulting in alterations in the paternal genome. Thus, COVID-19 has been demonstrated to impair sperm quality depending on the severity of the disease (He et al., 2021). This raises the question of whether the virus can be transmitted to the embryo through sperm.

Basigin (BSG) is known to be a critical factor in spermatogenesis. It has been reported that COVID-19 creates a new viral invasion pathway through S-protein binding to BSG (Mahdian et al., 2020), rather than only binding to ACE2 and TMPRSS2. Therefore, the role of BSG in the SARS-CoV-2 pathway is of interest. BSG is a glycoprotein (a transmembrane protein of vertebrate epithelial cells, also known as glycosylated transmembrane protein CD147 or extracellular matrix metalloproteinase inducer). It plays an important role in reproduction and is essential for normal fertility in both men and women. Disruption or inhibition of BSG by SARS-CoV-2 leads to impaired implantation of the embryo in the uterus. This novel invasion pathway of SARS-CoV-2 represents a potential new target for antiviral development.

Conclusion

A number of cells and tissues have been identified as targets for the pandemic virus (SARS-CoV-2). This allows us to explain the different symptoms in patients with COVID-19 and the long-lasting effects after infection. Damage to these cells has a different mechanism along with the general principles of the virus.

Author's note

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Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

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Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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