Review

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A survey of SARS-CoV-2 tropism

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has significantly burdened global public health. However, the tropism of SARS-CoV-2 within the human body remains not fully understood. In this review, we overview the literature on SARS-CoV-2 infection across various human organs and tissues. We summarize the relevant specimen types, techniques for examining SARS-CoV-2 tropism, and findings at both organ/tissue and cellular levels. To systematically evaluate the evidence supporting SARS-CoV-2 tissue tropism, we establish a hierarchical classification system based on two key criteria: (1) specimen origin and (2) detection methodology. Clinical specimens obtained directly from COVID-19 patients provide the most definitive evidence, whereas organoid-derived specimens and animal models indicate potential infectivity under artificial conditions. In terms of detection methods, we prioritize viral particle identification over viral protein or RNA detection, as the latter requires further confirmation to establish productive infection. Our findings indicate that SARS-CoV-2 potentially targets multiple human organ systems, including the respiratory tract, lungs, kidneys, heart, blood vessels, pancreas, small intestine, liver, and salivary glands. By contrast, viral tropism for the central nervous system and the reproductive system remains uncertain and requires further validation. At the cellular level, we identify specific target cell types vulnerable to infection, including ciliated epithelial cells, alveolar type II pneumocytes, enterocytes, cardiomyocytes, vascular endothelial cells, renal tubular epithelial cells, and pancreatic acinar cells. Furthermore, we analyze the correlation between angiotensin-converting enzyme 2 receptor distribution patterns and viral tropism, as well as potential variations in tissue specificity among different viral variants. We expect this review to provide a comprehensive landscape of SARS-CoV-2 tropism and enhance our understanding of the life cycle and consequences of SARS-CoV-2 infection within the human body.

Keywords: COVID-19; SARS-CoV-2; Tropism; Organoid; Autopsy

1. Overview of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease 2019 (COVID-19)

SARS-CoV-2 is a member of the beta coronavirus family and is a single-stranded, positive-sense RNA virus, sharing 79% genome sequence identity with SARS-CoV, the causative agent of the 2003 outbreak.[1] The SARS-CoV-2 virion comprises four structural proteins: nucleocapsid (N), membrane (M), envelope (E), and spike (S) proteins.[2] In addition to these structural components, the SARS-CoV-2 genome encodes various non-structural and accessory proteins critical for completing the virus's life cycle within the host cell.[3,4]

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The S protein of SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) receptor on the surface of target cells.[5] Following cleavage by transmembrane serine protease 2 (TMPRSS2), the S protein undergoes a conformational change that facilitates viral membrane fusion and entry into the host cell.[6] When TMPRSS2 expression is insufficient in target cells, the virus can alternatively enter via the cleaved S protein through cathepsin L (CTSL).[6,7] Additionally, studies indicate that neuropilin-1 (NRP1) and extracellular matrix metalloproteinase inducer (EMMPRIN, also known as CD147) significantly influence viral entry into host cells.[8,9] The broad expression of *ACE2* receptors in human tissues allows SARS-CoV-2 to initially infect the respiratory tract and subsequently spread to other organ systems, causing widespread systemic infection.[10]

COVID-19, caused by SARS-CoV-2, is a highly infectious disease with primary clinical symptoms including cough, fever, fatigue, headache, and sore throat.[11,12] Some patients may also present with neurological and gastrointestinal symptoms, such as loss of smell and taste, vomiting, and diarrhea.[13] In severe cases, the disease can progress to acute respiratory distress syndrome (ARDS) and widespread multi-organ damage.[11] Recent studies have identified that some individuals, even after recovering from the acute phase of COVID-19, experience persistent symptoms and complications. This condition is commonly referred to as long COVID, Post-Acute Sequelae of SARS-CoV-2 infection (PASC), or chronic COVID syndrome.[14,15]

2. Specimens and methods for detecting SARS-CoV-2 tropism

2.1. Specimen types

The initial step in investigating the tropism of SARS-CoV-2 involves acquiring appropriate study specimens.[16] In addition to collecting specimens directly from individuals diagnosed with COVID-19, recent technological advancements have enabled researchers to culture organoid structures that replicate specific organ functions and develop genetically modified animal models (Figure 1). In this section, we provide a general overview and summary of the concepts and functions of common specimens used in SARS-CoV-2 tropism studies.

2.1.1. Autopsy specimens

Autopsy, also known as a postmortem examination, involves the dissection, examination, and analysis of a deceased individual's body. The findings from an autopsy can reveal both pathological and physiological changes, allowing scientists to better understand the mechanisms and areas affected by disease development.[17,18]

Autopsy plays a particularly critical role in understanding the pathogenesis of emerging infectious diseases such as COVID-19, especially in the early stages when limited information is available about disease mechanisms and viral tissue tropism.[19] Autopsy specimens from individuals who died of COVID-19 serve as the primary resources for identifying the tissue tropism of SARS-CoV-2. These specimens can be analyzed using a range of techniques, including histological analysis, immunohistochemistry, in situ hybridization, electron microscopy, and multi-omics approaches, to investigate the distribution and abundance of the virus in various organs and tissues.[20,21] Such analyses offer a multi-dimensional perspective of COVID-19 and contribute to identifying distinct disease phenotypes. However, it is important to note that autopsies are typically performed on patients who succumbed to severe forms of COVID-19, and thus the findings may not fully represent all cases.

2.1.2. Biopsy specimens

Human tissues and cells derived from biopsies are crucial specimens for studying the tropism of pathogens within specific tissues and cells. These specimens are obtained through medical imaging-guided biopsy procedures, including puncture or endoscopy, which enable the extraction of specific tissues or cells from patients. Biopsies collected from COVID-19 patients and human *ex vivo* tissue cultures can provide valuable insights into the cellular and molecular changes underlying the disease. Such findings can aid in the development of effective treatments and diagnostic methods. However, due to the challenges in obtaining biopsies directly from COVID-19 patients, biopsies from donated organs or precancerous tissues can serve as reliable alternatives for research purposes.

2.1.3. Organoids

Organoid technology is an innovative biotechnological approach in which stem cells derived from embryonic or adult tissues are cultivated in a three-dimensional (3D) environment to recreate structures that closely mimic the architecture and function of specific organs or tissues.[22,23] The pluripotent differentiation potential of stem cells, combined with advancements in *in vitro* culture techniques, has enabled organoids to exhibit self-organization and self-renewal capabilities.[24] Two principal types of 3D-cultured organoid systems have been developed: those derived from human pluripotent stem cells and those generated from adult tissues.[25] Organoid technology has emerged as a vital research tool in translational medicine, cancer biology, and drug development. These models effectively replicate the pathophysiology of organs in disease states and were widely utilized in viral pathogenicity studies before the COVID-19 pandemic.[26] During the pandemic, organoid technology provided valuable research specimens and insights, helping to address many scientific challenges posed by SARS-CoV-2.[27] Nevertheless, it is important to acknowledge the limitations of organoid studies and interpret their results with caution.

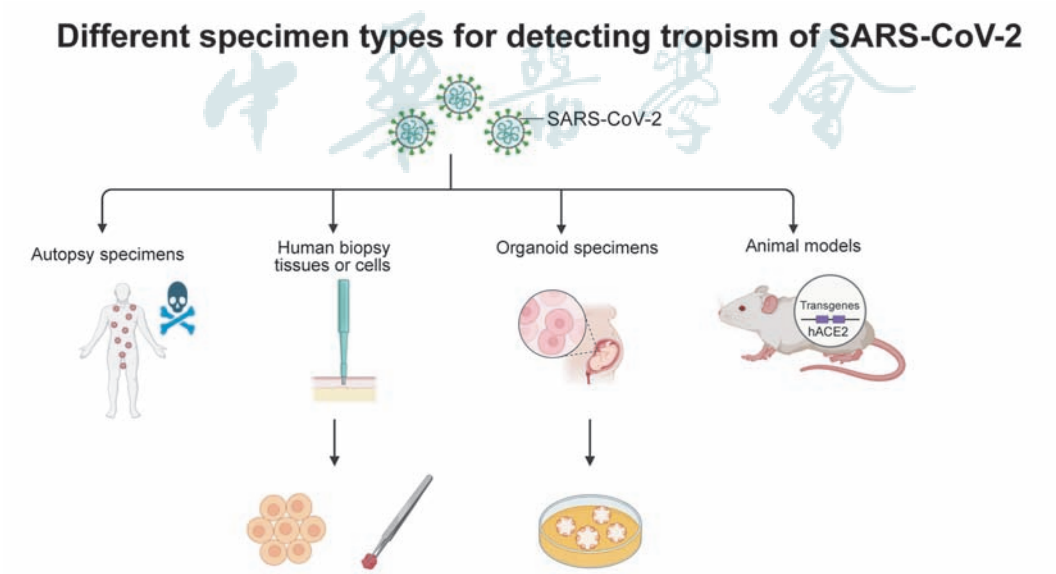

Figure 1: Various types of specimens are used to study the tissue tropism of SARS-CoV-2. The figure was created with Biorender.com. We classify our specimens into four categories: (1) postmortem specimens; (2) human biopsy specimens; (3) organoid model specimens; and (4) animal model specimens. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; hACE2: human angiotensin-converting enzyme 2.

2.1.4. Animal models

Animal models are experimental systems that utilize non-human species, such as rats or monkeys, to replicate the occurrence and progression of human diseases or specific biological processes. These models are widely used to assess the efficacy of vaccines and therapeutic drugs.[28] Due to their advantages—including short experimental durations, relatively low costs, and easy accessibility—animal models have become invaluable tools in investigating major human diseases.[28] They have been instrumental in the development of vaccines and therapeutics for SARS-CoV-2.[29,30] A diverse range of animal models has been used in SARS-CoV-2 research, including non-human primates (NHPs), genetically engineered mice, humanized mouse models, as well as Syrian hamsters, ferrets, poultry, and domestic animals.[30,31] While these models are designed to simulate virus-host interactions in humans, it is essential to acknowledge the inherent differences between species, which can introduce biases.

2.2. Methods for SARS-CoV-2 tropism research

Diverse techniques can be employed to detect the presence of SARS-CoV-2 in specific tissues, as detailed below (Figure 2). The presence of viral particles in specific specimens provides the strongest evidence of SARS-CoV-2's ability to infect the tissue. Detecting viral proteins suggests potential viral activity, while the detection of viral subgenomic RNA alone offers weaker evidence of viral replication within the tissue. Therefore, we recommend that readers consider both the specimen sources and assay methods used in other studies when evaluating SARS-CoV-2 tropism.

2.2.1. Detection of viral particles or infectious virus

Transmission electron microscopy (TEM) is an imaging technique that enables direct visualization of viral particles in tissues at the nanoscale level, making it a valuable tool for detecting SARS-CoV-2 infection.[32] However, the technique have significant limitations, including high costs, time-consuming procedures, and strict requirements for specimen preservation. Furthermore, accurately identifying viral particles at the subcellular level can be technically challenging and demands a high level of operator expertise.[33]

An alternative method for detecting infectious viral particles involves virus isolation and quantification. Techniques such as plaque assays and the 50% tissue culture infectious dose ($TCID_{50}$) assay are particularly effective when applied to fresh tissues or cultured cells.[34] The detection of live virus within a specific tissue or cell type offers compelling confirmation of viral tropism. Although virus isolation technology can precisely identify the presence and quantity of infectious virus, they are labor-intensive and reliant on high-quality samples, limiting their practicality for large-scale or multi-sample studies. Moreover, working with infectious virus requires access to high-level biosafety laboratories and strict specimen quality control to ensure the virus remains active throughout the testing process.[34]

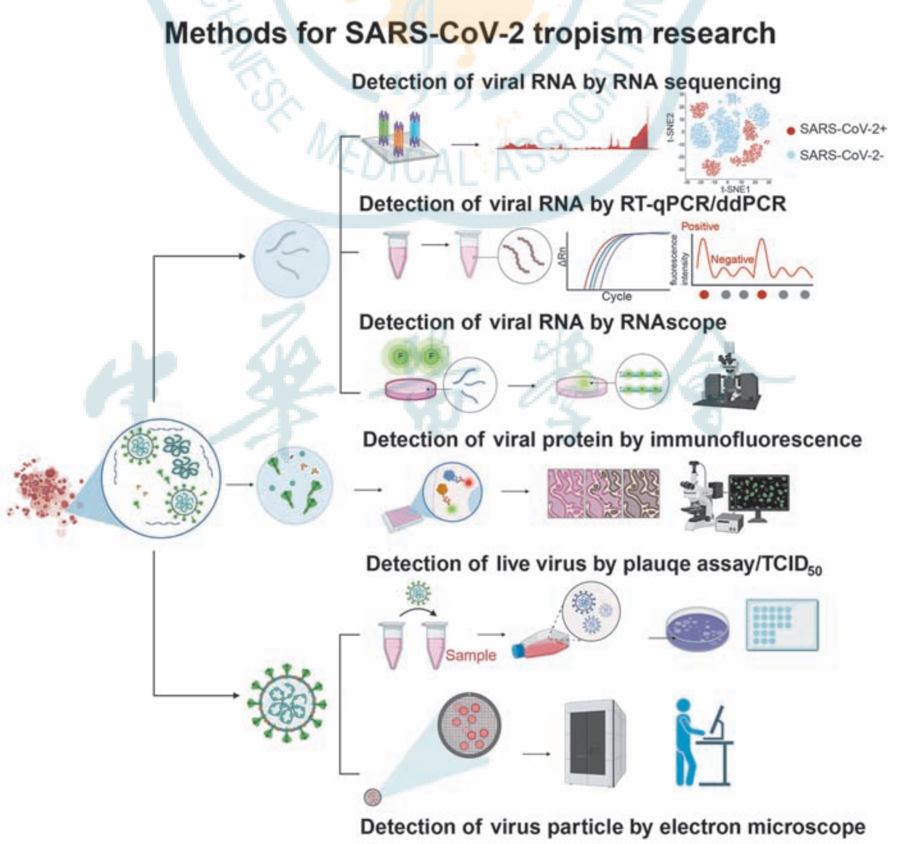

Figure 2: Strategies for detecting the tissue tropism of SARS-CoV-2 can be categorized based on the type of detection into intact viral particles, viral proteins, and viral RNA. This figure is created in https://BioRender.com. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; RT-qPCR: reverse transcription quantitative polymerase chain reaction; ddPCR: droplet digital polymerase chain reaction; $TCID_{50}$: 50% tissue culture infectious dose.

2.2.2. Detection of viral proteins

Immunohistochemistry is a technique that employs antigen–antibody interactions to detect the expression of specific proteins in tissues or cells.[35] This method is commonly applied to formalin-fixed paraffin-embedded tissues, which are easily stored and widely used across various biomedical research fields.[36] Immunofluorescence, a complementary technique, employs fluorescently labeled antibodies as molecular probes to detect target proteins in tissues.[37] By using multiple specific antibodies, immunofluorescence enables the simultaneous detection of several markers within a single tissue section. Visualization of the target proteins is achieved through laser scanning confocal microscopy, which provides high-resolution images of labeled proteins.[38,39] Both immunohistochemistry and immunofluorescence techniques are applicable to various types of specimens and can detect the presence of viral proteins in tissues (such as the SARS-CoV-2 N or S proteins) as a signal of viral infection in the tissue.[40,41] However, the detection of viral proteins does not confirm effective infection, as it could result from abortive infections or contamination under specific scenarios.[42]

2.2.3. Detection of viral RNA

Reverse transcription quantitative real-time PCR (RT-qPCR) is a highly sensitive and specific technique that was widely employed during the early stages of the COVID-19 pandemic to detect SARS-CoV-2 RNA in patient specimens, such as nasopharyngeal swabs, saliva, and bronchoalveolar lavage fluid.[43] This method is also capable of detecting viral RNA in specific tissues or cells, aiding in identifying the virus's tissue tropism and potential target organs. Another prominent detection method is digital droplet PCR (ddPCR), which uses water-in-oil emulsions to partition background DNA or RNA into thousands of individual droplets.[44,45] Technologies for quantifying viral nucleic acids, such as RT-qPCR and ddPCR, have demonstrated substantial potential for SARS-CoV-2 detection and represent promising diagnostic tools for the identification and surveillance of various infectious diseases.[46,47]

RNA in situ hybridization (RNA ISH) and RNAscope technologies are robust tools for visualizing and localizing RNA in specific tissues.[48,49] These techniques use molecular probes that bind to specific RNA sequences in fixed, permeabilized tissues or cells. After hybridization, the RNA–probe complex emits a fluorescent signal, enabling optical microscopy to detect the target RNA's presence and location.[50] Unlike PCR-based RNA detection methods, RNA ISH and RNAscope provide the added benefit of in situ tissue analysis, offering spatial context for RNA expression.[51]

However, the detection of viral RNA in specific tissues or cells does not necessarily confirm that the virus can complete processes such as genome replication, transcription, translation, virion assembly, and release within those tissues or cells. Positive viral RNA signals may result from abortive viral infections or specimen contamination. Probes targeting the negative-strand viral genome RNA are recommended to improve reliability, and combining RNA ISH or RNAscope with other detection technologies can help minimize false-positive results.

2.2.4. High-throughput sequencing-based methods

High-throughput sequencing and its derivative technologies enable rapid and efficient large-scale sequencing of DNA or RNA samples within a short timeframe.[52] Compared to bulk sequencing, single-cell sequencing and spatial single-cell sequencing provide single-cell and spatial resolution, respectively, offering unprecedented insights and broader perspectives.[53] By aligning sequencing data from specific tissues or cells to the SARS-CoV-2 reference genome, researchers can quantify viral RNA read counts to confirm its presence in a specimen.[54]

3. Tissue and cell tropism of SARS-CoV-2

Substantial evidence indicates that SARS-CoV-2 exhibits tropism for multiple organs and cell types.[55–74] In addition to the respiratory tract, vital organs such as the stomach, heart, and kidneys are at risk of viral infection. This study evaluates the susceptibility of various tissues to SARS-CoV-2 infection at both the tissue and cellular levels; the findings emphasize the necessity of robust evidence to confirm viral tissue tropism (Figure 3; Figure 4; Supplementary Table S1, http://links.lww.com/IDI/A62). Based on current evidence, we categorize SARS-CoV-2 target tissues or cells into three tiers: definitive infection (supported by ≥2 concordant studies demonstrating intact viral particles), probable infection (consistent detection of viral proteins without viral particles across studies), and unconfirmed infection (limited to viral RNA detection or where evidence remains contradictory).

3.1. Respiratory system

The respiratory system, comprising the trachea, airways, and distal alveoli, serves as the primary site for gas exchange between the internal and external environments.[75] It is a critical component of the human respiratory system, which is divided into the upper and lower respiratory tracts. The internal

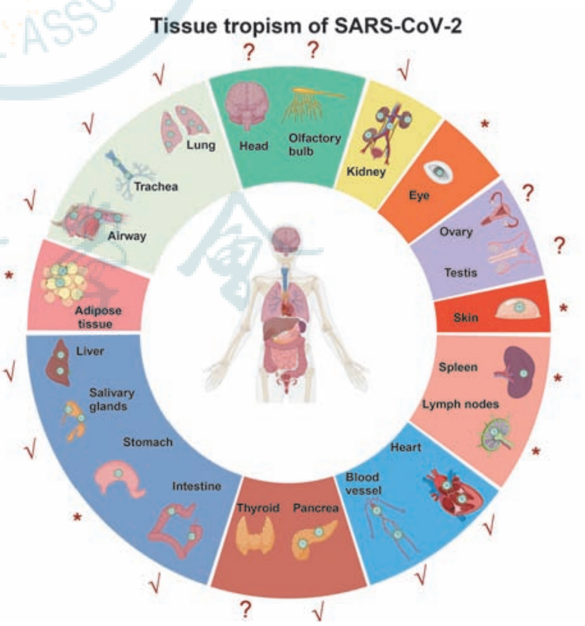

Figure 3: Overview of the tissue tropism of SARS-CoV-2 for various tissues. Definitive infection (√): viral particles or live virus have been detected in tissues from at least 2 studies without contradictory evidence. Probable infection (*): viral proteins have been detected in tissues from COVID-19 patients' specimens. Unconfirmed infection (?): Only viral RNA has been detected in tissues, or there is a lack of evidence regarding whether the virus can infect that tissue. This figure is created in https://BioRender.com. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

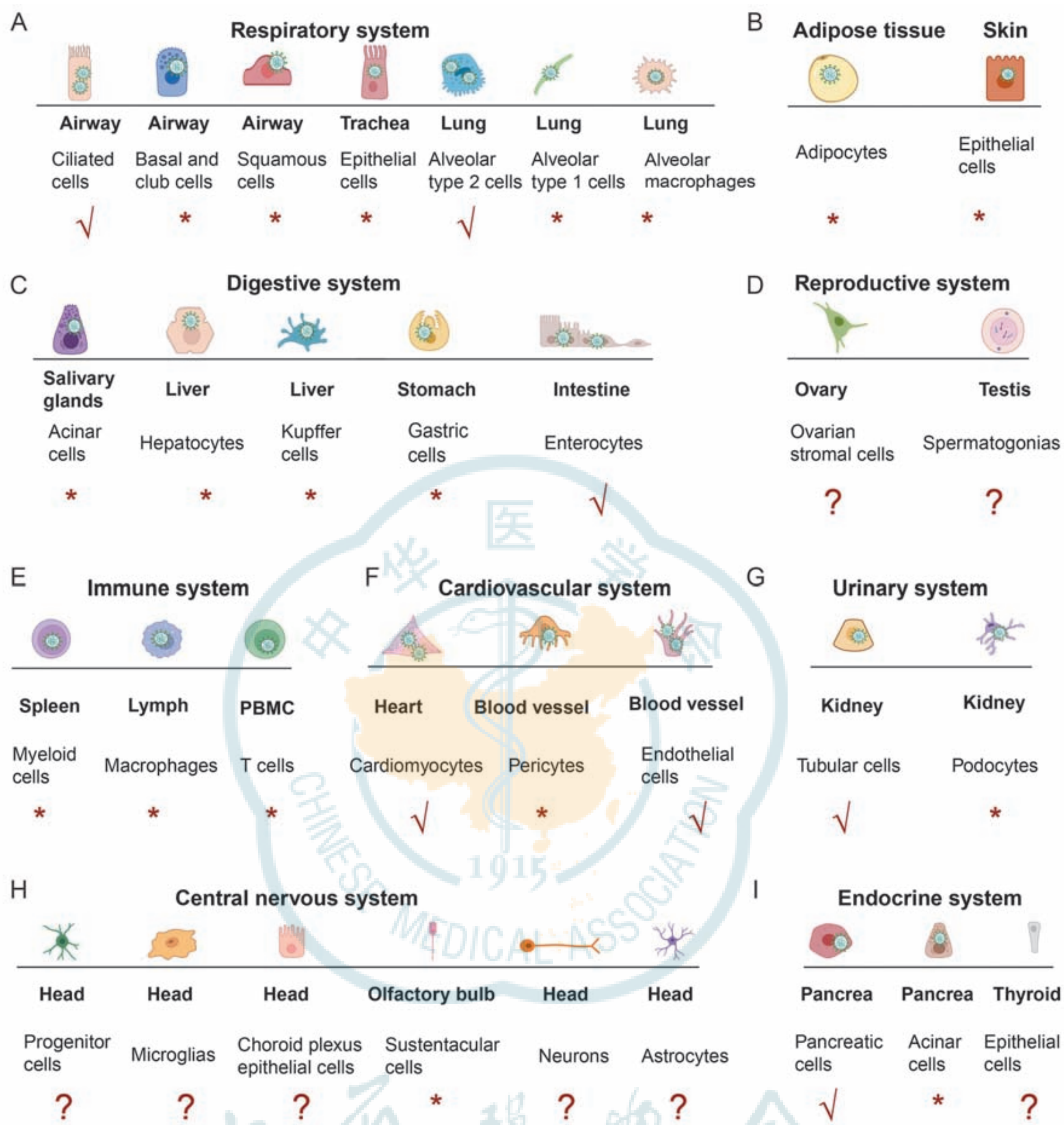

Figure 4: Overview of the tropism of SARS-CoV-2 for various cells. (A–I) Cell tropism of SARS-CoV-2 for different systems or tissues. Definitive infection (√): viral particles or live virus have been detected in cells from at least 2 studies without contradictory evidence. Probable infection (*): viral proteins have been detected in cells from COVID-19 patients' specimens. Unconfirmed infection (?): Only viral RNA has been detected in cells, or there is a lack of evidence regarding whether the virus can infect that tissue. This figure is created in https://BioRender.com.

microenvironment of the respiratory tract is highly complex, containing various specialized cell types, such as ciliated cells, macrophages, and endothelial cells. These cells are essential for maintaining normal respiratory function, clearing foreign particles, and defending against pathogenic infections.[76]

SARS-CoV-2 primarily targets the respiratory system, leading to clinical symptoms such as coughing and difficulty breathing. In severe cases, infection can progress to pneumonia or respiratory failure.[11] *ACE2* is widely expressed across various cell types in the trachea, airways, and alveoli.[77–79] This expression pattern underscores the broad potential for SARS-CoV-2 infection in the respiratory tract.

Research based on autopsies and organoid models has shown that the respiratory tract, including the trachea, airways, and lungs, is the primary target of SARS-CoV-2 infection. Ciliated cells and type II alveolar cells (AT2 cells) are the main target cells.[80–92] The detection of viral particles in these tissues and cells suggests that the virus can replicate and spread extensively within the respiratory system.[85,86,88] Additionally, other cell types, including secretory cells, squamous cells, goblet cells, basal cells in the upper airways, and alveolar macrophages in the lungs, may also become infected.[85,93] This is supported by the presence of viral proteins and subgenomic RNA in these cells, as observed in studies using autopsy and human-derived specimens.[41,83,94] While goblet cells (also known as club cells) have the potential to be infected by SARS-CoV-2, infections in these cells are rarely observed. This is likely due to the absence of viral replication components in goblet cells, which highlights the virus's preferential cell tropism.[95] Single-cell sequencing data from samples such as nasopharyngeal swabs and bronchoalveolar lavage fluid from COVID-19 patients further confirm that SARS-CoV-2 can infect ciliated cells, goblet cells, basal cells, and squamous cells.[54,96,97] Collectively, these studies demonstrate that SARS-CoV-2 exhibits a broad tropism for the respiratory system, which serves as the primary gateway for viral invasion and dissemination in the body.

Autopsy studies and investigations using human salivary gland organoids have also provided evidence of SARS-CoV-2 infection in the salivary glands. This includes the detection of infectious viral particles, viral proteins, and viral RNA.[121–123] Acinar cells have been identified as the primary targets within salivary glands infected by SARS-CoV-2.[121]

3.2. Digestive system

The human digestive system comprises the digestive tract and digestive glands. Some individuals infected with SARS-CoV-2 may present with gastrointestinal symptoms, including anorexia, diarrhea, vomiting, and abdominal pain.[98] Additionally, viral RNA has been detected in the feces of certain patients, suggesting the potential for fecal-oral transmission of SARS-CoV-2.[99–101] Interestingly, the expression levels of ACE2 in intestinal tissues are higher than those in the respiratory tract.[77,102]

Numerous studies have confirmed the tropism of SARS-CoV-2 for the digestive system. The presence of SARS-CoV-2 viral particles and proteins in human tissue specimens and intestinal organoid models derived from COVID-19 patients has been documented.[100,103–109] Furthermore, infectious viral particles have been successfully isolated from the feces of some patients.[107] Enterocytes have been identified as the primary target cells in the gastrointestinal tract, with multiple studies reporting the presence of viral particles or proteins in these cells.[100,101,103,104,107–109] Moreover, Giobbe et al. reported that gastric cells in human gastric organoid models can be infected by SARS-CoV-2, although in vivo evidence is lacking.[105] Animal model studies conducted by Jiao et al. corroborated the findings from human findings, identifying infection in the digestive tract and detecting viral particles and RNA in a primate model.[110] Investigations into bat organs have further revealed that SARS-CoV-2 can infect the intestinal tissues of bats.[107] Notably, bat intestinal tissues exhibit higher baseline expression of antiviral genes compared to human intestinal tissues, facilitating a faster and more robust innate immune response. This may contribute to the asymptomatic carrier state of the virus in bats.[111]

The liver, a vital digestive and endocrine organ, plays a central role in numerous physiological processes and is essential for maintaining homeostasis.[112] Liver injury is a common complication during SARS-CoV-2 infection, typically indicated by elevated levels of aspartate aminotransferase and gamma-glutamyl transferase.[113] These findings suggest that the liver can be directly affected by SARS-CoV-2 infection. Autopsy findings from COVID-19 patients have consistently shown the presence of viral particles, proteins, or RNA in liver tissues, supporting the liver's susceptibility to SARS-CoV-2.[40,93,114–117] Liver organoid studies have further confirmed the presence of SARS-CoV-2 viral particles in infected human liver organoids, reinforcing the notion that the liver is a target organ for the virus.[118] Hepatocytes, Kupffer cells, and endothelial cells have been identified as potential targets of SARS-CoV-2 infection. Several studies have provided compelling evidence of viral proteins in hepatocytes and Kupffer cells, underscoring their vulnerability.[40,114,115] Asialoglycoprotein receptor 1 has been identified as a key receptor for mediating viral entry into hepatocytes.[119] The detection of viral proteins in liver endothelial cells further supports their involvement in the infection process.[40,120]

3.3. Central nervous system

During SARS-CoV-2 infection, patients may experience a range of neurological symptoms, including reduced sense of smell and taste, dizziness, headaches, altered consciousness, and ataxia.[124] In severe cases, concurrent neurodegeneration, cerebral edema, and even encephalitis have been observed. The detection of SARS-CoV-2 in cerebrospinal fluid and brain tissue specimens from certain individuals suggests the potential for viral invasion of the nervous system.[116,125] Traditionally considered immune-privileged, the central nervous system (CNS) has now been shown to exhibit immune activity.[126] The CNS is protected by several physical barriers, including the meninges, the interface between the nasal epithelium and the olfactory bulb, the blood-cerebrospinal fluid barrier (BCSFB), and the blood-brain barrier (BBB).[127] These structures, together with resident immune cells, play a crucial role in preventing pathogen invasion.

Bauer et al. proposed a concise definition of neuroinvasiveness, referring to the ability of a virus to breach these physical barriers and access specific neural tissues or organs.[128] This concept is essential for evaluating whether SARS-CoV-2 can be classified as a neurotropic virus. One study demonstrated that non-infectious SARS-CoV-2 models were able to breach the blood-brain barrier in mouse models, leading to CNS involvement.[129] Research using human brain organoid and mouse models has further revealed viral infection in brain capillary endothelial-like cells, supporting the notion that SARS-CoV-2 has the ability to cross physical barriers.[130,131] Another potential pathway for SARS-CoV-2 entry into the CNS is through the respiratory tract, with possible infection of the olfactory bulb tissue.[128] While Khan et al. reported not infection of the olfactory bulb tissue, their findings did confirm viral infection in supporting cells of the olfactory epithelium.[90] This suggests that the virus may not traverse the olfactory epithelium to enter the CNS. By contrast, several studies have demonstrated SARS-CoV-2 infection in the olfactory bulb, indicating that the olfactory nerve could serve as a potential route for viral invasion into the nervous system.[132–134]

Studies utilizing human brain organoids provide compelling evidence of SARS-CoV-2 infectivity in CNS tissues and cells following viral entry.[135–143] In both organoid and animal models, viral particles, proteins, and RNA have been detected in neurons, astrocytes, and choroid plexus epithelial cells.[133,135–137,139–142,144] Additional findings show viral RNA or proteins in glial cells, microglia, and neural progenitor cells.[133,134,138,139,142] *ACE2* expression in neurons, astrocytes, and choroid plexus epithelial cells provides a molecular basis for SARS-CoV-2 infection in these cell types.[145,146] Postmortem studies of COVID-19 patients have revealed SARS-CoV-2 RNA in brain tissue, including the optic and olfactory nerves and the choroid plexus.[93,116,147–150] However, viral proteins were rarely detected,[123,151–153] and only one study provided evidence of SARS-CoV-2 viral particle detection.[115] In line with organoid findings, astrocytes and neurons were also found to be infected in autopsy specimens.[115,151] Interestingly, several studies have reported infection of cerebral blood vessels and vascular endothelial cells in the brain, with viral RNA or proteins detected in these cell types.[115,148,154,155]

Overall, CNS infection by SARS-CoV-2 appears to be an opportunistic event. Although the virus shows the potential to breach physical barriers and invade neural tissues, findings across studies have been inconsistent, suggesting that such events may be relatively rare.[90,156–158] Moreover, the detection of viral RNA in brain specimens alone is insufficient to confirm CNS infection. It is possible that systemic inflammation associated with COVID-19 compromises the integrity of the BBB or BCSFB, allowing viral RNA to enter the CNS without direct infection of neural tissues.[159]

3.4. Cardiovascular system

The cardiovascular system, comprising the heart and blood vessels, is recognized as a potential target for SARS-CoV-2 infection. COVID-19–associated symptoms such as arrhythmias and acute myocardial injury have been linked to poorer prognoses in affected individuals.[160] The heart, a complex organ with four chambers, is composed of diverse cell types, including cardiomyocytes, fibroblasts, endothelial cells, pericytes, smooth muscle cells, immune cells, adipocytes, and neural cells.[161] The high expression of *ACE2* in cardiac tissue suggests that the heart is particularly susceptible to SARS-CoV-2, identifying it as a potential target organ.[162] Viral particles, proteins, and RNA have been detected in the hearts of COVID-19 patients through autopsies and tissue specimens.[40,92,93,115,117,147,163–165] These findings are further substantiated by studies using human heart organoid models and animal models, which confirm that the heart can indeed be infected by SARS-CoV-2.[166–169] Among the cardiac cell types, cardiomyocytes have been identified as potential target cells for viral infection. Several studies have reported the presence of viral particles or proteins within cardiomyocytes,[115,163,164,166–168,170–172] as well as in pericytes, where viral proteins have also been detected.[171,173] These observations suggest that SARS-CoV-2 can directly infect and damage specific cell types in the heart.

Endothelial cells, which form the inner lining of blood vessels, are essential to cardiovascular function and have been identified as significant targets for SARS-CoV-2 infection.[174–176] Multiple studies have confirmed the virus's ability to infect blood vessels.[174,177] Recent research indicates that SARS-CoV-2 infection of endothelial cells triggers inflammatory responses, a process that plays a key role in the pathogenesis of COVID-19.[41,165]

Given the virus's pronounced tropism for endothelial cells, it is plausible that such cells across various organs may also become infected. This widespread endothelial involvement may contribute to multi-organ complications beyond the cardiovascular system. The infection of endothelial cells underscores the systemic nature of SARS-CoV-2 and highlights the importance of further research into its role in organ-specific complications.

In conclusion, strong evidence supports SARS-CoV-2's tropism for the human cardiovascular system. Recognizing the complex relationship between COVID-19 and cardiovascular health can help healthcare professionals develop more targeted interventions and treatment strategies. Ultimately, such insights are crucial for improving patient outcomes and mitigating the virus's impact on cardiovascular function during and beyond the course of the pandemic.

3.5. Urinary system

The urinary system, comprising the kidneys, bladder, and ureters, plays a central role in urine production and excretion. Among patients with COVID-19, acute kidney injury has emerged as a common complication, highlighting the susceptibility of the kidneys to SARS-CoV-2 infection and its associated damage.[178,179] The high expression of *ACE2* in renal tissue further supports this vulnerability.[180]

Evidence from autopsies, biopsies, and organoid models has confirmed the presence of viral particles, proteins, or RNA in kidneys affected by SARS-CoV-2.[40,93,115,117,150,181,182] Notably, Sun et al. isolated infectious viral particles from the urine of COVID-19 patients, raising the possibility of SARS-CoV-2 transmission via urine.[183] Interestingly, a diabetic environment appears to exacerbate the kidney's susceptibility to SARS-CoV-2, possibly due to altered energy metabolism and increased *ACE2* expression.[184] However, evidence regarding viral infection in the ureter and bladder remains limited. In most cases, renal tubular epithelial cells within the renal parenchyma are identified as the primary targets of viral infection.[93,115,185–187] In addition, viral RNA or proteins have been detected in other renal cell types, such as renal cells and podocytes.[185] In conclusion, a growing body of research supports the tropism of SARS-CoV-2 for the kidneys, with viral infection potentially contributing to renal fibrosis and severe kidney injury.[185]

3.6. Reproductive system

Our current understanding of SARS-CoV-2 infection in reproductive organs and its clinical implications remains limited. Few COVID-19 patients have reported symptoms related to the reproductive system.[188] While *ACE2* expression has been observed in the testes, ovaries, uterus, and vagina, it is not significantly expressed in the female reproductive system.[189,190]

Evidence suggests the possibility of SARS-CoV-2 invasion of reproductive tissues. Yao et al. reported the presence of viral RNA and proteins in the blood-testis barrier (BTB) in autopsy specimens from COVID-19 patients.[91] Two additional studies identified viral particles in the testes, with spermatogonial cells as the potential targets of infection.[117,191] Other studies have detected viral RNA or proteins in the testes, ovaries, and uterus.[91,93,117] Li et al. demonstrated that SARS-CoV-2 infection in hamsters led to acute testicular damage, although this damage was prevented by vaccination.[192] Peirouvi et al. provided evidence that SARS-CoV-2 can impair BTB function by reducing the expression of junctional proteins and increasing the expression of inflammatory factors.[193] This disruption may facilitate viral entry into the testis via the vasculature. While these findings support the potential for SARS-CoV-2 infection in reproductive organs, such infection appears to be a relatively rare clinical event rather than a typical manifestation of COVID-19.

The possibility of vertical transmission from mother to fetus remains uncertain. Limited and often conflicting evidence has led to ongoing debate.[194–198] Current research does not conclusively support SARS-CoV-2 infection of the placenta.[120,196,198,199] Further investigation is needed to assess the tropism of SARS-CoV-2 for reproductive tissues and to inform appropriate clinical treatment strategies.

3.7. Endocrine system

The organs of the endocrine system regulate various physiological functions, primarily through hormone secretion. Several endocrine organs—including the pancreas, salivary glands, thyroid, and thymus—are considered potential targets for SARS-CoV-2 infection.[147,200] Research has shown the presence of viral particles, proteins, or RNA in the pancreas.[148,201–204] A notably high frequency of infection has been observed in various pancreatic cell types, including islet alpha cells, beta cells, and other endocrine cells.[201–205] COVID-19 has also been associated with thyroid dysfunction. Studies by Poma et al. and Macedo et al. analyzed thyroid specimens from deceased COVID-19 patients and reported direct infection of the thyroid by SARS-CoV-2, with viral RNA localized in thyroid tissue.[206,207] Similarly, Rosichini et al. demonstrated infection of human primary thymic epithelial cells, suggesting that the thyroid and thymus may be targeted by SARS-CoV-2.[208] Despite these findings, the infection of endocrine organs by SARS-CoV-2 appears to be relatively rare.

3.8. Immune system

The potential for SARS-CoV-2 to infect immune cells and interfere with normal immune function remains a compelling area of investigation. As the respiratory system is the virus's primary point of entry, immune cells located within respiratory tissues are at risk of infection. Using single-cell sequencing, Ren et al. and Ziegler et al. identified viral RNA in various immune cell types, such as T cells, B cells, NK cells, macrophages, neutrophils, and plasma cells.[54,97] Further, multiple studies have confirmed the presence of viral antigens in alveolar macrophages, further supporting the idea that immune cells in the respiratory tract can be directly targeted by SARS-CoV-2.[80,91,115,120,209]

The spleen and lymph nodes, as peripheral lymphoid organs, are key sites for immune responses and are primary reservoirs for immune cells. SARS-CoV-2 infection of these organs has been demonstrated, with viral RNA or antigens detected in both tissues.[40,91,93,117,181] Certain immune cells within the spleen and lymph nodes also appear susceptible to infection.[40,91,93] These observations, derived from postmortem analyses, suggest that such infections are more common in severe cases of COVID-19.

Recent findings have also indicated the potential for SARS-CoV-2 to infect circulating lymphocytes in the blood, including monocyte macrophages, T cells, and B cells. Several studies have reported the presence of viral RNA or antigens in these cell types.[210,211] Notably, a study by Shen et al. identified infectious virus within T cells isolated from the peripheral blood of COVID-19 patients.[212] These findings suggest that circulating immune cells can be directly infected by SARS-CoV-2, highlighting the virus's potential to interfere with immune function and contribute to disease severity.

3.9. Other tissues and organs

SARS-CoV-2 has demonstrated the ability to infect various tissues and organs beyond the respiratory system, including adipose tissue and the eye. Several studies have shown that the virus can invade adipose cells, with evidence of viral particles or RNA detected in adipose tissue specimens.[213–215] Additionally, the virus has been detected in the eye, particularly in the cornea, retina, and vitreous body.[216–221] These findings raise the possibility that ocular routes may facilitate viral transmission. However, some studies have reported negative results for SARS-CoV-2 infection in the cornea,[222,223] suggesting that such infections are rare, and the likelihood of viral transmission through corneal transplants from deceased COVID-19 patients remains very low.

3.10. ACE2 and SARS-CoV-2 tropism

The ACE2 receptor serves as the decisive and indispensable factor mediating SARS-CoV-2 entry into host cells.[224,225] As a result, *ACE2* expression levels in specific tissues or cells are strongly associated with viral tropism.[226] Successful viral invasion and replication typically require two essential steps: (1) Access of the virus to the target tissue through specific mechanisms, and (2) sufficient expression of viral receptors—particularly *ACE2*—within the target tissue. Multiple studies have systematically analyzed *ACE2* expression profiles across various human tissues and cell types. Significant ACE2 expression has been identified in the intestinal epithelium, renal tubules, gallbladder, myocardium, testicular tissue, placenta, vascular endothelium, and hepatocytes,[77] with especially high levels observed in the small intestine, testes, kidneys, heart, thyroid, and adipose tissues.[180] These findings align with our investigation, as most of these tissues have been confirmed as targets for SARS-CoV-2 infection. Furthermore, a meta-analysis found that ACE2 levels were elevated in the respiratory epithelial cells of current and former smokers compared to nonsmokers.[227] Subsequent studies have corroborated that this ACE2 upregulation enhances host cell susceptibility to SARS-CoV-2 infection.[228]

4. SARS-CoV-2 variants and tropism

Since the onset of the pandemic, the continual emergence of SARS-CoV-2 variants has posed an ongoing challenge for global health organizations. To date, the World Health Organization (WHO) has designated five Variants of Concern (VOCs): Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Omicron (B.1.1.529).[229,230] Although the pandemic has been officially declared over, descendant lineages such as XBB, JN.1, and XEC continue to circulate in certain regions.[231] Emerging research indicates that JN.1, KP.3.1.1, and XEC variants possess enhanced abilities to evade humoral immunity and escape from receptor-binding domain-targeting antibodies.[231,232] However, further investigation is needed to determine whether these variants exhibit altered host tropism.

Current evidence suggests that SARS-CoV-2 evolution has influenced viral tropism, with Omicron variants exhibiting reduced pulmonary tropism compared to ancestral strains and earlier variants such as Alpha and Delta.[233] This phenotypic shift appears to be associated with two key factors: (1) Omicron exhibits reduced replication efficiency in pulmonary cells compared to earlier variants,[234,235] and (2) The virus exhibits prolonged persistence in nasal and sinus mucosal tissues, which may limit its penetration into the lower airways and reduce the risk of pulmonary inflammation.[236] A German autopsy study reported significantly higher nasal viral loads in Omicron cases compared to non-VOC lineages. However, no significant differences in viral loads were observed among different variants in other organs, including the lungs, blood, heart, liver, kidneys, and brain.[237] Currently, limited data are available regarding the tropism of different variants for non-respiratory tissues and organs. More comprehensive studies are required to fully characterize the tissue-specific tropism of various SARS-CoV-2 variants.

5. Conclusion

COVID-19, caused by SARS-CoV-2, continues to represent a major global health concern. With its potential for multi-organ involvement, the disease poses increased risks to vulnerable populations, particularly those with pre-existing conditions. This situation underscores the urgent need for the development of more effective vaccines and therapeutic strategies, especially in light of going emergence of new variants. Although the respiratory system is the primary target for the virus, SARS-CoV-2 exhibits a complex tropism affecting various tissue and cell types throughout the human body. Further research is essential to deepen our understanding of the specific mechanisms underlying the multisystem effects of SARS-CoV-2.

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Author Contributions

Jianwei Wang, Xianwen Ren and Lili Ren conceptualized and supervised the whole study, Xiangxing Jin searched the literature, contributed to the analysis and provided important scientific input. Xiangxing Jin, Lili Ren, Xianwen Ren and Jianwei Wang wrote the first draft and revised version of the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None.

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