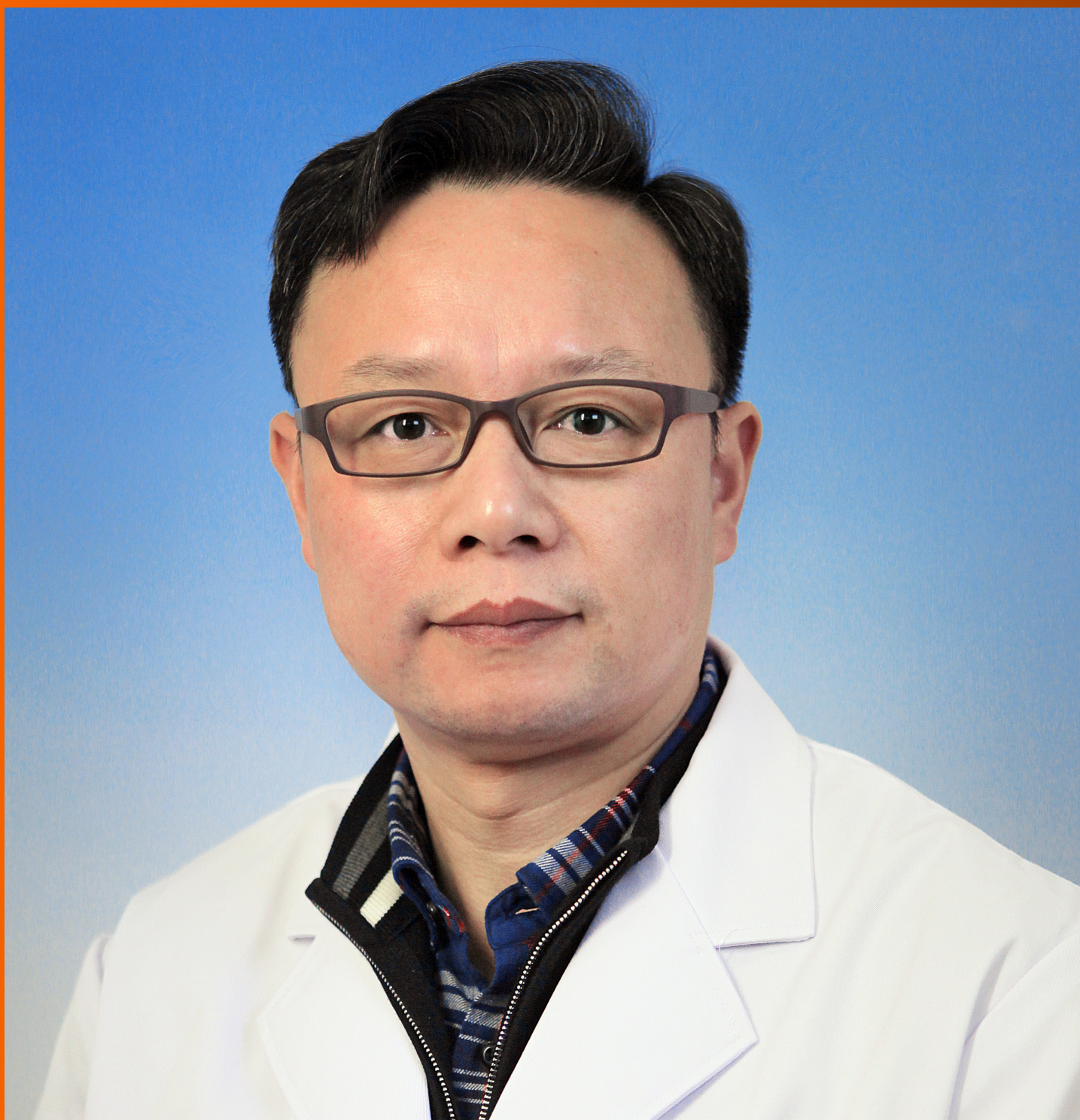


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Molecular mechanisms underlying SARS-CoV-2 hepatotropism and liver damage

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Abstract

In coronavirus disease 2019 (COVID-19), severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) primarily targets the respiratory system, but evidence suggests extrapulmonary organ involvement, notably in the liver. Viral RNA has been detected in hepatic tissues, and in situ hybridization revealed virions in blood vessels and endothelial cells. Electron microscopy confirmed viral particles in hepatocytes, emphasizing the need for understanding hepatotropism and direct cytopathic effects in COVID-19-related liver injury. Various factors contribute to liver injury, including direct cytotoxicity, vascular changes, inflammatory responses, immune reactions from COVID-19 and vaccinations, and drug-induced liver injury. Although a typical hepatitis presentation is not widely documented, elevated liver biochemical markers are common in hospitalized COVID-19 patients, primarily showing a hepatocellular pattern of elevation. Long-term studies suggest progressive cholestasis may affect 20% of patients with chronic liver disease post-SARS-CoV-2 infection. The molecular mechanisms underlying SARS-CoV-2 infection in the liver and the resulting liver damage are complex. This "Editorial" highlights the expression of the Angiotensin-converting enzyme-2 receptor in liver cells, the role of inflammatory responses, the impact of hypoxia, the involvement of the liver's vascular system, the infection of bile duct epithelial cells, the activation of hepatic stellate cells, and the contribution of monocyte-derived macrophages. It also mentions that pre-existing liver conditions can worsen the outcomes of COVID-19. Understanding the interaction of SARS-CoV-2 with the liver is still evolving, and further research is required.

Key Words: SARS-CoV-2; COVID-19; Hepatotropism; Angiotensin-converting enzyme-2

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Core Tip: The hepatotropism of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a growing concern amid the coronavirus disease 2019 (COVID-19) pandemic. Despite its respiratory focus, the virus significantly affects various organs, notably the liver, leading to complications like inflammation, abnormal function tests, and, in severe cases, organ damage. This complex involvement worsens disease outcomes. Understanding the virus's interplay with the liver, mediated by the Angiotensin-converting enzyme-2 receptor, is crucial for tailored treatments. The liver's pivotal role in the immune response emphasizes the need to comprehend SARS-CoV-2 hepatotropism. Ongoing research is vital for uncovering mechanisms, clinical implications, and effective strategies in managing COVID-19 patients with liver involvement.

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INTRODUCTION

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), belonging to the *Betacoronavirus* genus within the *Coronaviridae* family, is a positive-sense, single-stranded RNA virus with an enveloped structure. It shares close genetic relatedness with severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1) and Middle East respiratory syndrome CoV. The genome of SARS-CoV-2 is approximately 30000 base pairs long, encoding 16 nonstructural and 4 structural proteins, including spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins. The spike protein assumes a critical role in the SARS-CoV-2 life cycle by governing viral attachment, fusion, entry, and transmission. This glycoprotein contains the S1 and S2 domains as functional components able to act as ligands for receptor binding and downstream membrane fusion, respectively. Notably, the receptor binding domain within the S1 unit exhibits significant genetic variability within the coronavirus genome[1,2].

When it comes to infecting the majority of host cells, the SARS-CoV-2 spike engages with its primary receptor, Angiotensin-converting enzyme-2 (ACE2). The process is further facilitated by host transmembrane proteases, such as serine 2 [transmembrane serine protease 2 (TMPRSS2)], which play a crucial role in priming the spike protein for receptor interaction and subsequent entry into the host cell. In the facilitation of viral entry may also act additional host co-factors, such as neuropilin-1, glycosaminoglycans, C-type lectins, and furin. Noteworthy is the spike protein's specific binding to ACE2 and TMPRSS2, which collectively support viral entry. The differential expression of ACE2 and TMPRSS2 in various tissues, including the airways, lungs, nasal/oral mucosa, and intestine, underscores the multifaceted nature of the viral entry process across different cellular environments. The affinity of the spike protein for the ACE2 receptor plays a critical role in determining the replication fitness and severity of SARS-CoV-2 infection[1,2].

In the context of Coronavirus Disease 2019 (COVID-19), produced by the infection with SARS-CoV-2, the most profound pathological modifications are predominantly evident within the respiratory system. Nevertheless, it is of utmost significance to acknowledge that this viral infection imposes deleterious consequences on various other bodily organs. Notably, evidence has been presented of the presence of SARS-CoV-2 viral RNA in extrapulmonary organs, including the liver[3-6]. Building upon the excellent review conducted by Roshanshad *et al*[6], this editorial seeks to provide supplementary insights into the molecular mechanisms underlying SARS-CoV-2 hepatotropism and liver damage. The specific cellular location of viral replication remains unclear because of the use of whole-tissue homogenization techniques for nucleic acid extraction. Subsequent examinations, employing in situ hybridization analysis, identified the presence of SARS-CoV-2 virions within the lumen of blood vessels and endothelial cells in the portal veins of liver tissues derived from COVID-19 patients[7,8]. Furthermore, electron microscopic assessments of liver specimens from two COVID-19 patients who succumbed to the disease and exhibited elevated liver enzyme levels revealed the presence of intact viral particles within the cytoplasm of hepatocytes[9].

Although the precise etiology of liver injury in the context of COVID-19 remains partially understood, various factors have been postulated to contribute to this phenomenon (Figure 1), including direct cytotoxic effects, vascular changes, immunological and inflammatory responses associated with COVID-19, immune responses triggered by COVID-19 vaccination, and drug-induced liver injury (DILI)[10-12].

The assessment of hepatotropism concerning SARS-CoV-2 and the possible manifestation of direct cytopathic effects are crucial for a comprehensive understanding of the mechanisms underlying liver injury in COVID-19. It is worth noting that a typical hepatitis presentation has not been extensively documented[7,9,13], despite recent albeit limited discoveries.

The prevalence of elevated liver biochemical markers in individuals with COVID-19 varies in different studies but, in hospitalized patients, these abnormalities can be observed in the vast majority of them. These are primarily characterized by a hepatocellular pattern of elevation. The extent of these elevations is typically mild, and the likelihood of encountering substantial increases in alanine aminotransferase or aspartate aminotransferase levels (> 20-fold upper normal limit), liver synthetic dysfunction, or elevated serum bilirubin levels remains relatively uncommon among COVID-19 patients[14-17]. Remarkably, recent extended follow-up investigations have unveiled that after SARS-CoV-2 infection, progressive cholestasis may impact as many as 20% of individuals with chronic liver disease (CLD), demonstrating a proclivity toward increased severity[18].

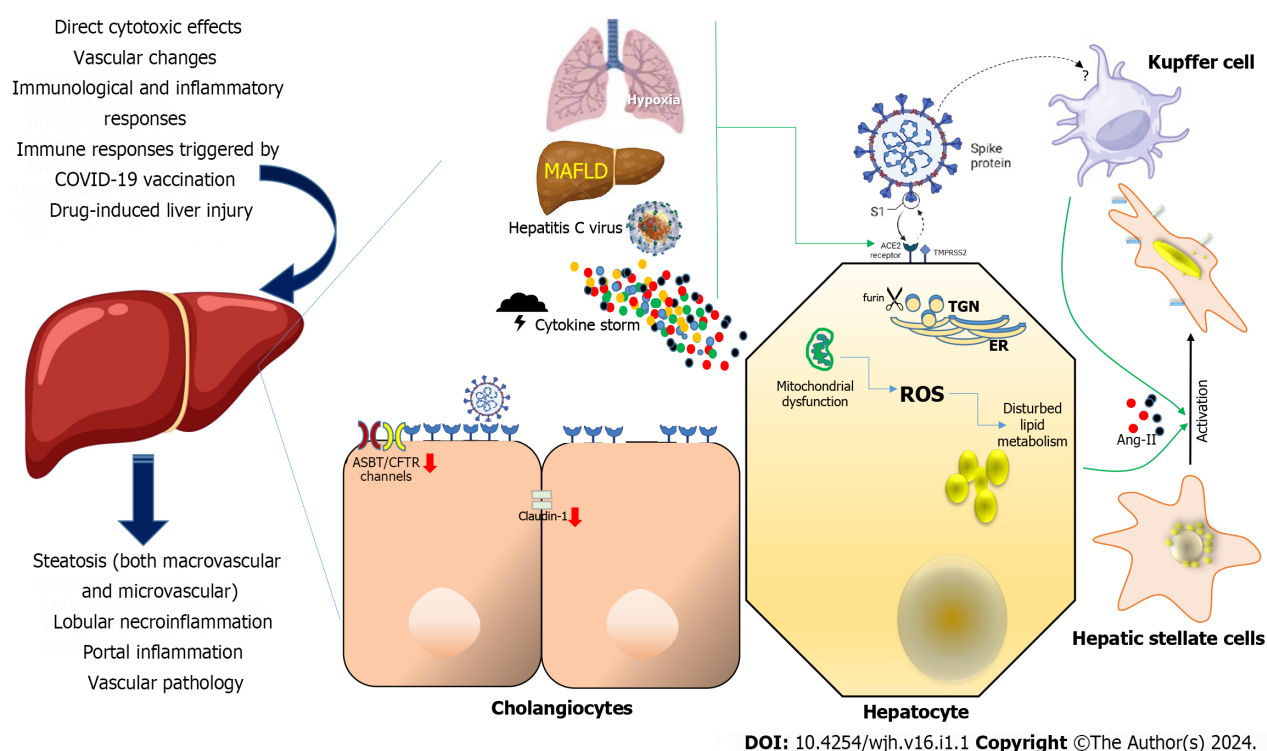


Figure 1 Mechanisms of severe acute respiratory syndrome coronavirus-2 disease-induced liver injury and their consequences at organ level (left). Severe acute respiratory syndrome coronavirus-2 cellular targets involved in liver damage (center and right). Various factors have been postulated to contribute to liver injury in the context of coronavirus disease 2019 (COVID-19), including direct cytotoxic effects, vascular changes, immunological and inflammatory responses associated with COVID-19, immune responses triggered by COVID-19 vaccination, and drug-induced liver injury. In the context of liver injury associated with COVID-19, the histological patterns encompass features such as steatosis (both macrovascular and microvascular), lobular necroinflammation, portal inflammation, and vascular pathology. At the cellular level, hypoxia, metabolic dysfunction-associated fatty liver disease, and concomitant hepatitis C virus infection, and the cytokine storm may upregulate the Angiotensin-converting enzyme-2 (ACE2), transmembrane serine protease 2 and furin expression in hepatocytes. Mitochondrial dysfunction has been affected directly by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection of hepatocytes which in turn may be connected to pre-existing inflammation and the adverse impacts of excessive and dysfunctional adipose tissue. In cholangiocytes, SARS-CoV-2 Leads to a decrease in the mRNA expression of Claudin-1 and downregulates the expression of hepatobiliary transporters, such as ASBT and the chloride channel CFTR. The ACE-2 expression in Kupffer cells is still controversial. Hepatic stellate cells appear do not express ACE2 in any activation state. Their activation is a pivotal event in the progression of chronic liver disease, as these cells serve as the primary source of fibrosis, and it is induced by proinflammatory and profibrotic signals, including angiotensin II, which is generated by the catalytic action of ACE as part of the profibrotic branch of the renin-angiotensin system. Liver and Kupffer cell are created with BioRender.com. ROS: Reactive oxygen species; ACE2: Angiotensin-converting enzyme-2; TMPRSS2: Transmembrane serine protease 2; MAFLD: metabolic dysfunction-associated fatty liver disease; ER: Endoplasmic reticulum; TGN: Trans-Golgi network.

ACE2 AND VIRAL ENTRY CO-FACTORS EXPRESSION IN HEPATIC CELLS CONTRIBUTING TO SARS-COV-2 HEPATOTROPISM

A comprehensive understanding of tissue reservoirs supporting SARS-CoV-2 replication remains a critical research challenge. This is, in part, attributed to the inherent challenges associated with procuring biopsy samples from individuals presently infected with the virus, coupled with the requisite use of high-level laboratory containment facilities. The well-established understanding includes the interaction of the viral spike protein (S) with ACE2 for cellular entry, emphasizing the crucial roles of TMPRSS2 and furin enzymes in the infection process[1]. Consequently, examination of the expression of these receptors during the early stages of infection provided valuable insights into the potential permissiveness of hepatic cells. Notably, the liver exhibits minimal expression of ACE2 and TMPRSS2 proteins, whereas their highest expression is observed in the intestine and gall bladder. However, it is noteworthy that ACE2 expression appears to be absent in the lungs, where infection unequivocally occurs. Then, studies using single-cell RNA sequencing to analyze samples from healthy human livers revealed that although hepatic ACE2 expression is relatively low but still detectable. The expression level in cholangiocytes, the epithelium lining the bile duct, is similar to that found in lung alveolar cells[12,19]. Interestingly, sinusoidal endothelial cells appear to lack ACE2 expression, which aligns with earlier findings resembling SARS-CoV-1[20]. Recent observations concerning SARS-CoV-2-induced endothelitis in major intrahepatic arteries, coupled with the heightened presence of ACE2 in other endothelial cell types, such as those within the central and portal veins, which are similarly susceptible to infection by the virus, suggest the potential significance of this discovery[7]. TMPRSS2 and furin gene expression are broadly distributed across various liver cell types[21]. Notably, when three distinct single-cell RNA sequencing datasets from healthy liver tissue were collectively analyzed, it was observed that very few hepatocytes co-expressed both ACE2 and TMPRSS2[22].

To investigate the susceptibility of liver cell types to SARS-CoV-2 infection, experimental models involving cellular and organoid cultures have played a pivotal role. Hepatocellular carcinoma-derived cell lines such as Huh-7 and HepG2 have demonstrated the ability to support the entire viral life cycle[23]. A significant expression of ACE2 and TMPRSS2 in liver parenchymal cells was reported using bioinformatic analyses from a single-cell transcriptome database[21]. Permissiveness was demonstrated when pseudotyped lentiviral particles expressing the full-length spike protein of SARS-CoV-2 were inoculated to primary hepatocytes obtained from ACE2-humanized mice[24].

Importantly, research conducted in both murine and human subjects has revealed an increase in hepatic ACE2 expression within hepatocytes in the presence of liver fibrosis or cirrhosis, as already documented[25]. This finding holds significant relevance because pre-existing liver injury may exacerbate the susceptibility of hepatic tissues to the hepatitis C virus, SARS-CoV-2[26]. The impact of liver injury and pre-existing liver conditions on the propensity of SARS-CoV-2 to target the liver is still not well understood, and there is a notable absence of studies that have specifically investigated the histological alterations occurring in individuals with both COVID-19 and CLD. However, it is worth noting that previous investigations conducted before the emergence of COVID-19 have reported a significantly more than 30-fold elevation in ACE2 expression within the livers of patients suffering from cirrhosis related to the hepatitis C virus compared to individuals without underlying liver conditions[25,27] (Figure 1). These findings may be associated with the gene expression patterns observed in metabolic dysfunction-associated fatty liver disease (MAFLD), previously known as non-alcoholic fatty liver disease[28]. The presence of MAFLD within the broader context of metabolic syndrome may contribute to the exacerbation of COVID-19 severity. Molecular investigations have revealed elevated expression levels of crucial viral entry receptors, including ACE2, furin, and TMPRSS2, in individuals diagnosed with MAFLD. Furthermore, the liver mRNA expression of ACE2 and TMPRSS2 was found to be upregulated in individuals without active infection. Moreover, in obese patients with MAFLD, there was an observed upregulation of ACE2 in the liver as well as in subcutaneous and visceral adipose tissues compared with obese individuals lacking MAFLD[17,29,30] (Figure 1).

In addition, it has been established that hypoxia, a characteristic feature of severe cases of COVID-19, serves as a key regulatory factor in the upregulation of ACE2 expression in hepatocytes[17,25,31,32] (Figure 1). This phenomenon may explain the prevalence of extrapulmonary dissemination of SARS-CoV-2 in patients experiencing acute respiratory distress syndrome and other hypoxic conditions. Notably, in a manner analogous to findings in other organ systems, it is conceivable that inflammatory conditions and diseases affecting the liver, as reported[33,34], could elevate the expression of ACE2. Given the potential implication of DILI in the development of liver damage in COVID-19 patients[35,36], it is particularly interesting to investigate whether such conditions or specific pharmaceutical agents may induce excessive ACE2 expression within the hepatic environment. In contrast, while not yet substantiated in human subjects, Brevini *et al* [37] have recently delineated in a murine model the potential of ursodeoxycholic acid to inhibit ACE2, suggesting its potential as a promising therapeutic and prophylactic strategy against SARS-CoV-2.

In vitro experiments have demonstrated that the spike (S) protein of beta-coronaviruses exhibits a significant increase in its binding affinity for its receptor when it is pre-incubated with trypsin, a process involving proteolytic activation[1]. It's worth noting that liver epithelial cells express trypsin[38] and various other serine proteases, which are continuously involved in extracellular matrix remodeling and liver regeneration[39]. Considering this scenario, there is a plausible suggestion that the expression of ACE2, a pivotal factor for the precise targeting and recognition of SARS-CoV-2 within the liver, might be comparatively diminished in comparison to other tissues where extracellular proteolytic activity is less pronounced[40,41].

In concordance with these findings, recent discoveries have brought attention to the existence of a furin-like proteolytic site within the S protein of SARS-CoV-2, a feature not found in other coronaviruses belonging to the same lineage[1]. It is interesting to note that furin expression is mostly observed in organs that are hypothesized to be susceptible to SARS-CoV-2 infection. These organs include the pancreas, kidney, liver, and salivary glands[21].

ACE2-INDEPENDENT SARS-COV-2 HEPATOTROPISM

While our understanding of the tissue-specific determinants governing SARS-CoV-2 infection remains limited, there is a growing recognition of the involvement of additional accessory receptors in viral entry. Notably, studies have suggested that the high-density lipoprotein scavenger receptor B type 1 (SR-B1) plays a facilitating role in ACE2-dependent coronavirus attachment *in vitro*, drawing parallels with hepatitis C virus infection. Likewise, therapeutic interventions targeting SR-B1 have shown efficacy in mitigating the lipoprotein-mediated enhancement of SARS-CoV-2 infection. It is important to note, however, that using immunohistochemistry analysis of liver tissue was confirmed only sporadic ACE2 expression within the hepatic tissue[42]. Besides, it is crucial to acknowledge that additional factors, such as ganglioside (GM1)[43], may influence the interaction between the spike (S) protein and ACE2. Consequently, there is an imperative need for more comprehensive research into the S protein-ACE2 interactome to gain a deeper understanding of the molecular mechanisms involved and explore potential therapeutic avenues.

Ou *et al*[44,45] used pseudovirions carrying the spike (S) protein of SARS-CoV-2 to assess their ability to infect various cell lines. When exposed to viral vectors expressing the SARS-CoV-2 S protein, HuH7 and Calu3 cells (a cell line originating from human lung cancer) were more susceptible to transfection than reference pseudovirus. Additionally, these investigations suggested that the PIKfyve-TCP2 endocytotic pathway, which is expressed at lung-like levels in the liver and gall bladder[15], could be important for the viral entry process[46].

EXPERIMENTAL MODELS FOR STUDYING SARS-COV-2 HEPATOTROPISM

HuH7 cells has been reported as a permissive model to develop a novel and effective functional viromics screening method to forecast the possibility of zoonotic occurrences with known lineage B betacoronaviruses. This model was employed to investigate the binding and recognition processes of both SARS-CoV-1 and SARS-CoV-2[47]. This approach further confirmed the affinity of SARS-CoV-2 for hepatocytes. It is important to note that in their study, HuH7 cells were identified as the third most permissive cell line, following pulmonary (Calu3) and intestinal (CaCo₂) cell models, which represent organs with histopathological evidence of SARS-CoV-2 infection[47]. However, it is important to recognize that a cell's ability to attach and internalize viral particles does not always indicate that the particular cell type is also supportive of efficient viral reproduction. In this regard, it has shown that HuH7 cells indeed facilitate SARS-CoV-2 viral multiplication[23,48]. It has been determined that hepatocyte cell lines are robust permissive cell types for infections with SARS-CoV-1 and SARS-CoV-2. Notably, HuH7 cells have recently been used in SARS-CoV-2 immunostaining assays as a positive control[49]. It is essential to underscore that the findings suggesting hepatocytes as potential hosts for SARS-CoV-2 primarily stem from studies conducted with cancer cell lines. To establish the clinical relevance of these observations, it is crucial to conduct a comparison of ACE2 protein expression in HuH7 cells with that observed in primary human hepatocytes.

Post-mortem autopsies have yielded evidence supporting the concept of direct infection of liver cells by SARS-CoV-2. Several studies have recorded the identification of SARS-CoV-2 in a notable portion of post-mortem liver biopsies, employing techniques such as PCR and *in situ* hybridization. However, the direct invasion of hepatocytes by the virus was not consistently confirmed. Nonetheless, certain researchers managed to demonstrate the presence of distinct coronavirus particles, including spike structures, within the cytoplasm of hepatocytes in individuals with COVID-19. These observations were accompanied by signs of mitochondrial swelling and apoptosis, suggesting a potential link between the virus and cellular damage in the liver[7,9,50]. The diverse spectrum of histological injury patterns observed in individuals infected with SARS-CoV-2, including features such as macrovascular and microvascular steatosis, lobular necroinflammation, portal inflammation, and vascular pathology (Figure 1), likely emphasizes the intricate and multifactorial nature underlying abnormal liver test results in the context of COVID-19-associated liver injury[14-16,51]. Perhaps the most compelling evidence of SARS-CoV-2's ability to infect liver tissue was recently presented by Wanner *et al*[52]. In their study, the authors presented multiple lines of evidence for SARS-CoV-2 liver tropism, including the direct identification of SARS-CoV-2 genomic material within hepatocytes using *in situ* hybridization. In our study and theirs, infectious SARS-CoV-2 was isolated from post-mortem liver tissue[53]. Furthermore, Wanner *et al*[52] delineated activity profiles through transcriptomic and proteomic analyses in hepatic samples, affirming the presence of established SARS-CoV-2 entry receptors and facilitators of infection, encompassing ACE2, TMPRSS2, procathepsin L, and the Ras-related protein Rab-7a. The analyses also unveiled pronounced upregulation in interferon responses, JAK-STAT signaling, and liver-specific metabolic modulation. These findings collectively suggest a viral activity profile bearing notable resemblances to other hepatotropic viral infections, notably hepatitis C virus infection[52]. Moreover, it is imperative to conduct further investigations aimed at unraveling the molecular alterations initiated in hepatocytes subsequent to SARS-CoV-2 infection.

Valuable insights into this matter can be derived from the research conducted by Yang *et al*[54]. Using organoids created from human hepatocytes generated from pluripotent stem cells and primary adult human hepatocytes, their work confirmed SARS-CoV-2 hepatotropism. Using these organoids, the S-expressing pseudovirus of SARS-CoV-2 demonstrated the ability to infect human hepatocytes, leading to substantial viral replication. Additionally, gene expression analyses indicated that primary hepatocytes infected with SARS-CoV-2 exhibited heightened expression of pro-inflammatory cytokines, coupled with the downregulation of essential metabolic functions, as evidenced by the inhibition of CYP7A1, CYP2A6, CYP1A2, and CYP2D6 expression[54]. Wang *et al*[9] made a noteworthy advancement when they used electron microscope imaging to examine liver tissues from two deceased COVID-19 patients. They found that the hepatocytes they studied had viral structures that resembled SARS-CoV-2 virions. This data suggests that, even in the absence of a traditional hepatitis pattern, the histological alterations seen in these individuals might be the result of SARS-CoV-2's direct cytopathic effects[55]. It is important, therefore, that more research utilizing more extensive biopsy or autopsy cohorts in conjunction with all-encompassing imaging methods, including immunological electron microscopy, could be necessary to validate these preliminary findings about the existence of SARS-CoV-2 in hepatocytes [56].

THE RELEVANCE OF CHOLANGIOCYTES AS SARS-COV-2 CELLULAR TARGET IN LIVER

Bile duct epithelial cells, also referred to as cholangiocytes, fulfill pivotal functions in both the generation and regulation of bile, while also contributing to immune responses[57]. Single-cell sequencing of long-term liver ductal organoid cultures derived from human tissues revealed the persistence of ACE2 and TMPRSS2 expression[58] (Figure 1). Cholangiocytes were infected with SARS-CoV-2, causing syncytia formation. Twenty-four hours after the infection, there was a notable rise in the amount of SARS-CoV-2 genomic RNA. When the virus was inoculated to adult human cholangiocyte organoids, similar outcomes were seen, thus showing that SARS-CoV-2 infection *in vitro* may occur in human liver ductal organoids[54], raising the possibility of viral replication within the bile duct epithelium *in vivo*. Despite the notably elevated expression of ACE2 in cholangiocytes compared to hepatocytes, there are no reports of direct proof of SARS-CoV-2 infection in cholangiocytes in COVID-19 patients. Since hepatocytes and cholangiocytes are the primary producers of bile and because biliary fluids and cholangiocytes' apical membrane interact directly and continuously, the presence of

SARS-CoV-2 viral RNA or proteins in bile may be an indirect indicator of cholangiocyte SARS-CoV-2 infection. Currently, there is just one case report that shows SARS-CoV-2 RNA exists in bile, while bile samples from two other small sample series tested negative. Such disparities could be attributed to the circumstance that the bile sample yielding a positive result was obtained during the surgical resolution of bile duct obstruction, whereas the bile sample yielding a negative result was obtained from post-mortem autopsies conducted 48 h after death[59,60].

Tight junctions are essential for cholangiocytes to act as a barrier that protects parenchymal liver cells from potentially hazardous components of bile. Notably, *in vitro* studies have shown that viral infection with SARS-CoV-2 leads to a decrease in the mRNA expression of tight junction proteins such as claudin 1 in cholangiocytes, implying a compromised barrier function of these cells[58]. This disruption could result in liver injury, because it may allow toxic bile components to leak into the periductal space and adjacent liver parenchyma. Furthermore, SARS-CoV-2 infection downregulates the expression of hepatobiliary transporters, such as SLC10A2/ASBT and the chloride channel ABCC7/CFTR[58](Figure 1). This downregulation of hepatobiliary transporters could compromise the sensing and signaling of bile acids by cholangiocytes and the secretion of bicarbonate. Consequently, this could contribute to the identified biliary changes in individuals with COVID-19[61]. Additionally, inflammatory pathways were increased in SARS-CoV-2 infected cholangiocytes, indicating the establishment of a reactive phenotype[54]. Prospective investigation is needed to investigate if and how SARS-CoV-2 promoted cytokine production favoring inflammation and fibrosis, potentially playing a role in the development of the "reactive cholangiocyte phenotype". Such alterations have the potential to propagate inflammation and fibrosis[57].

ARE KUPFFER CELLS AND HEPATIC STELLATE CELLS SUSCEPTIBLE TO SARS-COV-2 INFECTION?

Alveolar macrophages and monocyte-derived macrophages (MDM) are known to express ACE2, and immunohistochemistry has revealed evidence of viral protein infection of alveolar macrophages caused by both SARS-CoV-1 and SARS-CoV-2[62-64]. Nonetheless, during a histopathological assessment of ACE2 tissue distribution, no staining for ACE2 was detected in Kupffer cells and other hepatic immune cells, despite the typical observation of Kupffer cell proliferation in the livers of individuals with COVID-19[9,65] (Figure 1).

Recent investigations in response to the COVID-19 pandemic have involved more comprehensive examinations of ACE2 expression patterns. These investigations included *de novo* single-cell RNA sequencing analyses and *in silico* evaluations of RNA sequencing databases. The results of these studies have consistently shown that Kupffer cells do not express ACE2. In contrast, a recent report that differentiates ACE2 expression in tissue macrophages demonstrated a high level of expression even among Kupffer cells[65]. However, it is crucial to emphasize that the evidence and findings reported thus far are based on samples from healthy human livers. Therefore, it may be necessary to quantify ACE2 expression in samples taken from individuals who had either an acute liver injury or underlying chronic liver illness to gain a more comprehensive understanding of different patterns of ACE2 expression in macrophages under such conditions[65,66].

It is worth noting that following liver injury or Kupffer cell depletion, MDM can infiltrate the liver and efficiently replenish the resident hepatic macrophage population[67-69]. While *in vitro* observations have indicated that MDM may not efficiently support the replication of SARS-CoV-1 (and likely SARS-CoV-2), infected MDM could serve as carriers of the pathogen, facilitating the infection of ACE2-expressing cells in the affected organ[70]. Additionally, Kupffer cell activation and proliferation are commonly observed due to systemic inflammation, and Kupffer cell activation has been reported in liver specimens from deceased COVID-19 patients. Through the propagation of inflammatory signals, monocytic cells may be important in SARS-CoV-2-mediated liver damage, even if ACE2 expression among Kupffer cells is a matter of debate[64].

Pre-existing chronic liver diseases seem to be independent risk factors associated with unfavorable outcomes in COVID-19, with the cirrhosis grade identified as a predictor of mortality in patients infected with SARS-CoV-2[71]. Since hepatic stellate cells are the main source of fibrosis, their activation is a crucial step in the development of chronic liver disease[72,73]. Activation is induced by proinflammatory and profibrotic signals, including angiotensin II, and arises fibrosis through the enzymatic activity of ACE within the profibrotic segment of the renin-angiotensin system[74] (Figure 1). Interestingly, ACE2 acts as an antagonist to ACE, generating the anti-inflammatory and anti-fibrotic peptide angiotensin-(1-7) and lowering the ratio of angiotensin II to angiotensin-(1-7) as a result[74]. Nevertheless, neither fibrogenic nor activated cells nor quiescent hepatic stellate cells have been shown to express ACE2[74-76]. These findings imply that these cells may not serve as highly permissive hosts for SARS-CoV-2. Nevertheless, the pro-inflammatory environment instigated by direct or indirect injury to hepatocytes and cholangiocytes in the context of COVID-19 may establish conditions conducive to the activation of hepatic stellate cells, thereby initiating the process of fibrosis (Figure 1). This scenario may be particularly pertinent for individuals who have already underlying chronic liver diseases, such as MAFLD as a condition characterized by steatosis in > 5% of the liver parenchyma. While available data indicate that liver injury caused by COVID-19 is typically mild and temporary, long-term surveillance studies are essential to fully assess the possibility of hepatic fibrosis developing as a long-term effect of COVID-19, especially in patients with pre-existing liver diseases. In the context of MAFLD, inflamed hepatocytes, along with other somatic cells, may manifest mitochondrial dysfunction[77,78]. Conversely, SARS-CoV-2 has been observed to directly impact mitochondrial function in hepatocytes[79] (Figure 1). Individuals with these conditions may undergo liver injury and exhibit elevated liver function tests due to direct viral cytotoxicity. Nevertheless, liver injury in these individuals may also be associated with pre-existing inflammation and the detrimental effects of excessive and dysfunctional adipose tissue. The interconnected influences of these factors may synergistically contribute to a more severe progression of both MAFLD and COVID-19.

Another pathogenic mechanism involves additional fat accumulation in hepatocytes triggered by SARS-CoV-2. COVID-19 induces dyslipidemia[80], and autopsy studies reveal a high prevalence of steatosis in COVID-19 patients[9,81,82]. As mentioned before, individuals with MAFLD exhibit elevated levels of ACE2 and various serine proteases in the liver[30], suggesting that preexisting steatosis may enhance susceptibility to COVID-19-induced damage. Reciprocally, COVID-19 may exacerbate existing steatosis. The quantitative significance of these dynamics remains uncertain and warrants further investigation in future research[83,84].

CONCLUSION

The understanding of the interaction of SARS-CoV-2 with the liver is still evolving, and more research is needed to fully elucidate the molecular mechanisms involved in liver tropism and damage in COVID-19. The complexity of these mechanisms underscores the importance of monitoring and managing liver function in patients with COVID-19, particularly those with underlying liver conditions.

FOOTNOTES

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