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COVID-19 and the liver: an adverse outcome pathway perspective

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ABSTRACT

Liver damage is observed in up to half of hospitalized COVID-19 patients and can result either from actions of SARS-CoV-2 as such or from pharmacological treatment. The present paper introduces an adverse outcome pathway construct that mechanistically describes the pathways induced by SARS-CoV-2 leading to liver injury. This can be caused by direct binding of the virus and local actions in cholangiocytes, but may also indirectly result from the general state of hypoxia and systemic inflammation in COVID-19 patients. Further research is urgently needed to fill remaining knowledge gaps. This will be anticipated to create a solid basis for future and more targeted development of vaccines and, in particular, therapies.

1. Introduction

More than 120 million people around the world were infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and 2.7 million individuals died as a consequence of the resulting coronavirus disease 2019 (COVID-19) early 2021 (https://coronavirus.jhu.edu/). One of the most frequent complications of COVID-19 is pneumonia (Vinken, 2020a). Nevertheless, in many cases, other organs are affected by SARS-CoV-2 as well. Among those is the liver, which in general is a frequent target for disease and toxicity because of its unique location and function in the body. However, the exact role and relevance of the liver in COVID-19 remains elusive. Adverse outcome pathway (AOP) constructs could be useful tools to assist in the mechanistic elucidation of the involvement of liver pathology in COVID-19. An AOP is activated following interaction of foreign entities with a biological system, referred to as the molecular initiating event (MIE). This induces a series of key events (KEs), linked through key event relationships (KERs) at different levels of biological organization, ranging from the molecular to the organism level, resulting in the actual adverse outcome (AO) (Ankley et al., 2010; Vinken et al., 2017). In this context, the Joint Research Centre of the European Commission started an interdisciplinary project called CIAO (modelling the pathogenesis of COVID-19 using the AOP framework), aiming at providing an overarching knowledge entry point to COVID-19 research separating signal from noise and giving scientists the possibility to quickly grasp dependencies between research fields not normally collaborating through the AOP concept (https://ec.europa.eu/jrc/en/event/webinar/intro-webinar-ciao-project). One of the many adversities scrutinized in CIAO is liver injury, which is documented in the present paper.

2. COVID-19 and the liver

2.1. Clinical features

The incidence of liver injury in COVID-19 ranges between 14.8 %–53 %, mainly manifested as abnormal aminotransferase levels that may go up to 3 times the upper limit of normal (Cai et al., 2020; Metawea et al., 2021). However, this may not only arise from the liver, but can equally originate from other organs, such as the muscles (Bangash et al., 2020). Many patients also show an increase in gamma glutamyl transferase serum amounts to 3 times the upper limit of normal, which points to cholangiocyte injury. Increases in alkaline phosphatase serum levels seem less common (Cai et al., 2020; Shao et al., 2020). Liver biopsy specimens of deceased COVID-19 patients indicate moderate microvascular steatosis, mild lobular and portal activity (*i.e.* necrosis, inflammation and/or fibrosis) (Ji et al., 2020; Schmit et al., 2021; Xu et al., 2020) as well as cholestasis (Schmit et al., 2021). Overall, the incidence of liver injury is higher in patients with severe COVID-19 compared to patients with mild symptoms and may even predict mortality

Abbreviations: ACE2, angiotensin-converting enzyme 2; AO(P), adverse outcome (pathway); CIAO, modelling the pathogenesis of COVID-19 using the AOP framework; COVID-19, corona virus disease 2019; IFN, gamma interferon gamma; KE(R), key event (relationship); MIE, molecular initiating event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TMPRSS2, transmembrane serine protease 2; TNF, alphatumor necrosis factor alpha.

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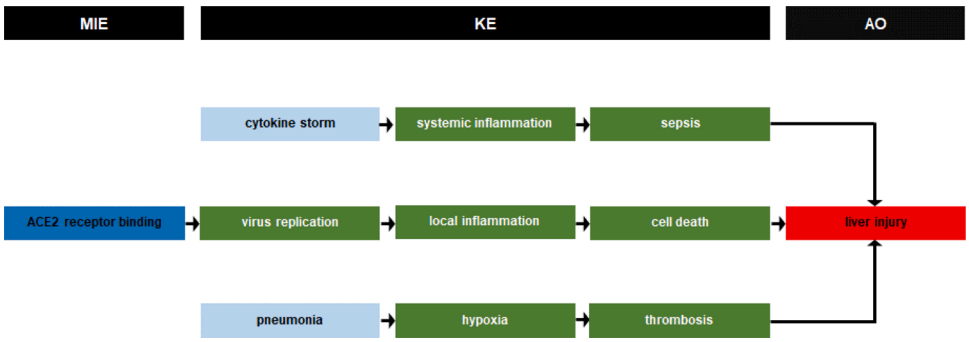

Fig. 1. Adverse outcome pathway describing the effects of COVID-19 on the liver (*ACE2, angiotensin-converting enzyme 2; AO, adverse outcome; KE, key event; MIE, molecular initiating event*).

(Boregowda et al., 2020; Hundt et al., 2020; Parohan et al., 2020; Piano et al., 2020). In fact, elder (Li et al., 2020a; Yu et al., 2020) and male (Feng et al., 2020; Kaushik et al., 2020) COVID-19 patients seem most prone to develop liver damage. Patients with pre-existing liver pathologies, in particular non-alcoholic steatohepatitis or metabolic-associated fatty liver disease, show higher liver injury in the course of the disease (Chen et al., 2021; Gao et al., 2021; Pan et al., 2021), yet others were not able to establish a link between chronic liver disease and mortality/severity of COVID-19 (Lippi et al., 2021; Palomar-Lever et al., 2020).

2.2. Mechanisms

Liver injury in COVID-19 can result either from actions of SARS-CoV-2 as such (*i.e.* pathology) or from pharmacological treatment (*i.e.* therapy). Regarding the latter, several drugs used in the clinical management of COVID-19 are known to trigger liver injury in patients, including lopinavir/ritonavir (Cai et al., 2020; Fan et al., 2020), hydroxychloroquine (Falcão et al., 2020) and remdesivir (Grein et al., 2020). Such drug-induced hepatotoxicity typically manifests as steatotic (*i.e.* fat accumulation) or cholestatic (*i.e.* bile acid accumulation) liver injury, all for which well-established AOPs are available (https://aopwiki.org/). As much as 59.7 % of the total cholangiocyte population expresses the angiotensin-converting enzyme 2 (ACE2) receptor, which facilitates cellular entry of SARS-CoV-2, a level that equals ACE2 receptor quantities measured in lung alveolar type 2 cells (Chai et al., 2020). Therefore, SARS-CoV-2 could directly target and enter cholangiocytes, resulting in viral replication and local cytopathic effects. *In vitro* experiments with human hepatocyte and cholangiocyte organoids indeed show infection with SARS-CoV-2 leading to virus replication (Yang et al., 2020; Zhao et al., 2020). Liver damage in COVID-19 may also occur indirectly as part of the severe systemic inflammatory response (*i.e.* cytokine storm) following SARS-CoV-2 infection. This is shown by a significant increase in serum levels of inflammatory markers, such as C-reactive protein, ferritin, lactate dehydrogenase, d-dimer, interleukins 2 and 6 (Chen et al., 2020; Ponti et al., 2020; Zhou et al., 2020a). In this light, sepsis and associated multi-organ failure underlie the cause of death in about one third of COVID-19 patients. Furthermore, liver damage in COVID-19 may be indirectly caused by oxygen deprivation in patients, which in turn results from pneumonia (Vinken et al., 2020a). This state of hypoxia is known to be permissive for the formation of microthrombi, *in casu* in liver, which can induce tissue damage (Pilli et al., 2018).

2.3. Adverse outcome pathway

A putative AOP depicting the mechanisms underlying the impact of COVID-19 on liver is proposed based on present knowledge and relevant literature data (Fig. 1). This AOP only takes pathology-related mechanisms, and thus not the adverse liver effects of therapy, into consideration. A total of 3 pathways lead to 3 liver injury, namely 1 direct pathway (*i.e.* triggered by the binding of SARS-CoV-2 to cholangiocyte ACE2 receptors) and 2 indirect pathways (*i.e.* triggered by the binding of SARS-CoV-2 to extrahepatic ACE2 receptors). In contrast to the former, the indirect pathways are preceded by a number of systemic adverse effects with MIEs located in other organs(s), which ultimately hit the liver. The data substantiating each of the KERs, and hence KEs, originate from various *in silico*, *in vitro, ex vivo*, *in vivo* and clinical studies (Table 1).

3. Outlook

AOPs have multiple applications, most of them in the area of toxicology and chemical risk assessment, such as in chemical categorization, test prioritization/de-risking strategies, development of *in vitro* and *in silico* assays, and establishment of integrated approaches to testing and assessment (Vinken et al., 2017). Nevertheless, AOPs also have their value in a clinical context. Indeed, AOPs can serve the development and optimization of clinically relevant animal models of disease for fundamental and translational research as well as for testing new therapeutics, and can aid the characterization of novel diagnostic and prognostic biomarkers of disease (Vinken, 2020b). In this respect, the CIAO project intends to model the pathogenesis of COVID-19 in view of facilitating the further development of vaccines and therapies (https://ec.europa.eu/jrc/en/event/webinar/intro-webinar-ciao-project). The pathways leading to COVID-19-related injury in the liver only represent a piece in this mechanistic puzzle and need to be linked to other critical mechanisms induced by SARS-CoV-2 in the body. It remains to be investigated how specific the effects of SARS-CoV-2 on the liver actually are and thus if the liver represents a primary target in COVID-19 *per se*. While SARS-CoV-2 directly binds and acts in cholangiocytes, the outcome of COVID-19 in liver equally results from the general state of hypoxia and systemic inflammation, which as such may affect all organs. AOPs are able to identify such knowledge gaps and therefore help to set future research priorities. By doing so, new scientific information will be generated that can be fed into the nascent AOP and that will either substantiate existing KERs and KEs, or that will identify new ones. It is anticipated that this will ultimately lead to thorough understanding of the mechanisms driving COVID-19, which in turn will form a solid basis for the further and more targeted development of vaccines and, in particular, therapies.

CRediT authorship contribution statement

Mathieu Vinken: Conceptualization, Methodology, Resources, Writing - original draft, Writing - review & editing, Visualization.

Declaration of Competing Interest

The author declares that he has no known competing financial

Table 1
Data substantiating key events and their relationships in the adverse outcome pathway describing the effects of COVID-19 on the liver (*ACE2, angiotensin-converting enzyme 2; IFN gamma, interferon gamma; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TMPRSS2, transmembrane serine protease 2; TNF alpha, tumor necrosis factor alpha*).

Key event relationship	Data	Type of study	Reference
ACE2 receptor binding (cholangiocyte) → virus replication	As much as 59.7 % of the total human cholangiocyte population expresses ACE2 receptor, which is much higher than hepatocytes (*i.e.* 2.6 % of cells) and that equals the level of ACE2 receptor expression in lung alveolar type 2 cells	*Ex vivo* study (analysis of human tissue samples)	Chai et al., 2020
	High expression of ACE2 receptor, TMPRSS2 and furin proteases in human cholangiocytes	*In silico* study/*ex vivo* study (analysis of human tissue samples)	Zhou et al., 2020b
	High expression of ACE2 receptor in human cholangiocytes	*In silico* study	Qi et al., 2020
ACE2 receptor binding (liver) → virus replication Virus replication → inflammation (liver)	Human hepatocyte and cholangiocyte organoids can be infected with SARS-CoV-2 leading to virus replication, upregulated expression of chemokines and downregulated expression of functional markers	*In vitro* study (human hepatocyte and cholangiocyte organoids)	Yang et al., 2020
Inflammation (liver) → cell death (pyroptosis/ necroptosis/ apoptosis)	TNF alpha and IFN gamma produced during SARS-CoV-2 infection induce pyroptosis, necroptosis and apoptosis	*In vitro* study (mouse and human macrophages)/*in vivo* study (mouse)	Karki et al., 2020
	SARS-CoV-2 infection activates apoptosis and necroptosis	*In vitro* study (human lung cells)/ *in vivo* study (mouse)/clinical study (COVID-19 patients)	Li et al., 2020b
ACE2 receptor binding (liver) → virus replication Cell death (pyroptosis/ necroptosis/ apoptosis) → liver injury	SARS-CoV-2-infected hepatocytes in livers of COVID-19 patients display apoptosis	Clinical study (COVID-19 patients)	Wang et al., 2020
	Human liver ductal organoids can be infected with SARS-CoV-2 leading to virus replication, cell death and dysfunctioning of cholangiocytes	*In vitro* study (human liver ductal organoids)	Zhao et al., 2020
Inflammation (systemic) → sepsis Sepsis → liver injury	COVID-19 patients with abnormal liver function tests show higher systemic inflammation and organ dysfunction	Clinical study (COVID-19 patients)	Piano et al., 2020
	COVID19 patients with severe inflammation are more likely to develop liver injury	Clinical study (COVID-19 patients)	Fu et al., 2021
	Liver injury in COVID-19 patients is associated systemic inflammation	Clinical study (COVID-19 patients)	Chu et al., 2020
	The severity of liver injury in COVID-19 patients is directly related to the incidence of sepsis	Clinical study (COVID-19 patients)	Sun et al., 2020
	Abundance of cytokines in COVID-19 patients is positively related to the incidence of liver injury	Clinical study (COVID-19 patients)	Zhang et al., 2020
Hypoxia → thrombosis Thrombosis → liver injury	Hypoxia increases the risk of thrombosis	*In vitro* study (HepG2 cells)/*in vivo* study (mouse)	Pilli et al., 2018
	Hypoxia promotes deep vein thrombosis	*In vivo* study (mouse)	Brill et al., 2013
	Elevation-associated hypoxia is an independent prothrombotic risk factor	Clinical study (*polycythemia vera* patients)	Zangari et al., 2013
	COVID-19 patients with hypoxia are more likely to develop liver injury	Clinical study (COVID-19 patients)	Fu et al., 2021
	Liver injury in COVID-19 patients is associated with hypoxia	Clinical study (COVID-19 patients)	Chu et al., 2020
	Livers of COVID-19 patients show thrombosis in portal and sinusoidal vessels	Clinical study (COVID-19 patients)	Sonzogni et al., 2020
	Livers of COVID-19 patients show thrombosis in central veins	Clinical study (COVID-19 patients)	Lax et al., 2020
	Liver dysfunction in COVID-19 patients is induced by microvascular thrombosis	Clinical study (COVID-19 patients)	Tsutsumi et al., 2021
	Thrombosis in COVID-19 patients is associated with liver dysfunction	Clinical study (COVID-19 patients)	Brosnahan et al., 2021

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