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LETTER TO THE EDITOR

The application of direct viral cytopathic hypothesis to design drug trials in the battle against COVID-19

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Abstract

COVID-19 has caused many deaths worldwide. Systemic complications alongside coagulopathy, and ARDS account for the majority of COVID-19 mortalities. The pathogenesis of the disease can be explained by two theories of direct viral cytopathy and systemic inflammatory cascade of events. ACE-2 is shown to be the cellular host receptor for SARS-CoV-2. It might be the key to explain the pathogenesis of systemic complications with a focus on the direct viral cytopathic hypothesis. Different medications tend to show up in many in vitro drug screens. However, more trials are needed to translate their application into in vivo efficacy.

Keywords Coronavirus disease of 2019 (COVID-19) · Potential therapies · Direct viral cytopathy

Introduction

Coronavirus disease of 2019 (COVID-19) has caused over 315,000 deaths worldwide. Although coronavirus-severe acute respiratory syndrome (SARS) and coronavirus-Middle East respiratory syndrome (MERS) have higher mortality rates than COVID-19, the rapid spread of COVID-19 has caused more overall deaths [1]. Different factors are responsible for the mortality in COVID-19. Acute respiratory distress syndrome (ARDS) is counted as the leading cause of mortality in severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), as well as in COVID-19 [2–4]. However, other factors also contribute to COVID-19 related deaths. Shi et al. showed a significant higher risk of cardiac injury among patients [5] .In addition, Li et al. reported acute kidney injury as an important predictor of mortality [6]. Overall, the pathogenesis of the disease can broadly be described by two theories, including direct viral cytopathy and the systemic inflammatory cascade of events.

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Discussion

Oudit et al. extracted SARS-CoV viral RNA from 35% of infected patients' cardiac tissue upon autopsy [7]. SARS-CoV virus fragments were reported in urine and blood specimens of infected patients [8]. Furthermore, Su et al. detected SARS-CoV-2 in kidney tissue [9]. Xu et al. investigation on a COVID-19 patient's liver biopsy specimen raised the possibility of direct injury due to SARS-CoV-2 virus [10]. These studies allow us to postulate that COVID-19 is not just a respiratory disease, but a multi-systemic syndrome involving lungs, kidneys, heart, and other ACE-2 positive organs.

ACE-2 is shown to be one cellular host receptor for SARS-CoV-2, similar to SARS-CoV [11]. ACE-2 might be important in the etiology of lethal complications and findings in COVID-19 patients. ACE-2 expressing organs seem to be the main targets in COVID19. Expression of ACE-2 was observed within the renal tubules, myocardial cells, alveolar cells of the lungs, enterocytes, and the endothelium, as well as the brain and the oral mucosal lymphocytes [12, 13]. Lethal complications, including ARDS, acute kidney injury, acute cardiac injury, and lymphocytopenia, might be explained by these observations.

The main focus of this letter is on direct viral cytopathic theory to explain the pathogenesis of COVID19. Considering this theory alongside multi-systemic inflammatory cascade theory can revolutionize the management of COVID-19 and its complications.

ACE-2 blockade is one method of blocking viral entry and further tissue damage. The proposed mechanism of viral entry upon ACE-2 binding of Spike-1 is endocytosis mediated by

clathrin. However, targeting the virus's endocytic pathways and viral replication might be effective in mitigating lethal complications. As previously shown, clathrin-mediated endocytosis is the main pathway for virus entry, while double-membrane vesicles formation and autophagy in the host cell is the mechanism for viral replication [14]. Chlorpromazine approved by USFDA as an antipsychotic medication, with minimal side effects, including dizziness and dry mouth inhibits clathrin-mediated endocytic pathway and has previously been shown to inhibit the entry of SARS-CoV and MERSCoV.

Transmembrane protease, serine 2 (TMPRSS2) is another factor facilitating SARS-CoV and MERS-CoV entry into the cell [16]. In MERS-CoV, furin-mediated precleavage at the S1/S2 site in infected cells might promote subsequent TMPRSS2-dependent entry into target cells [17]. Nafamostat, a clinically proven protease inhibitor, inhibits TMPRSS2 with a half-life of 8 min and can reduce the severity of the disease based on direct viral cytopathic theory [16].

Imatinib, a protein-tyrosine kinase inhibitor that inhibits the BCR-ABL tyrosine kinase which is approved to treat chronic myeloid leukemia by inhibiting ABL oncogenetic pathway has previously shown success in disrupting the viral entry mechanism of both SARS-CoV and MERS-CoV into the cell; hence, it can also be considered as a potentially useful drug to treat patients with severe forms of COVID-19.

Conclusion

Therefore, trialing the use of clathrin-dependent endocytosis inhibitors and lysosomotropic agents seem to be an option [14–16]. Moreover, previous in vitro studies have shown benefits of Nafamostat, a TMPRSS2 inhibitor, and Imatinib, an ABL oncogenetic pathway inhibitor in disrupting the viral entry mechanisms of SARS-CoV and MERS-CoV; hence these drugs may possibly prove to be effective in targeting direct viral cytopathy of SARS-CoV-2 [14, 16–18]. Ultimately, all these options can be considered alongside drugs that target specific steps in the lifecycle of RNA viruses for there to be a chance of efficacy in treating COVID-19 patients.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

References

1. Ruan S. Likelihood of survival of coronavirus disease 2019. Lancet Infect Dis. 2020;20:630–1. https://doi.org/10.1016/s1473-3099(20)30257-7.
2. Kim E, Choe P, Park W, et al. Clinical progression and cytokine profiles of middle EastRespiratory syndrome coronavirus infection. J Korean Med Sci. 2016;31:1717–25.
3. Lew T. Acute respiratory distress syndrome in critically ill patients with severe acute respiratory syndrome. JAMA. 2003;290:374–80.
4. Wu C, Chen X, Cai Y, Xia J', Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020;180:934. https://doi.org/10.1001/jamainternmed.2020.0994.
5. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol. 2020;5:802. https://doi.org/10.1001/jamacardio.2020.0950.
6. Li Z, Wu M, Yao J, Guo J, Liao X, Song S, et al. Caution on kidney dysfunctions of COVID-19 patients. SSRN Electron J. 2020. https://doi.org/10.2139/ssrn.3559601.
7. Oudit G, Kassiri Z, Jiang C, et al. SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. Eur J Clin Investig. 2009;39:618–25.
8. Peiris J, Chu C, Cheng V, Chan KS, Hung IF, Poon LL, et al. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. Lancet. 2003;361:1767–72.
9. Su H, Yang M, Wan C, Yi LX, Tang F, Zhu HY, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. Kidney Int. 2020;98:219–27. https://doi.org/10.1016/j.kint.2020.04.003.
10. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020a;8(4):420–2.
11. Tai W, He L, Zhang X, Pu J, Voronin D, Jiang S, et al. Characterization of the receptor-binding domain (RBD) of 2019 novel coronavirus: implication for development of RBD protein as a viral attachment inhibitor and vaccine. Cell Mol Immunol. 2020;17:613–20. https://doi.org/10.1038/s41423-020-0400-4.
12. Song R, Preston G, Yosypiv I. Ontogeny of angiotensin-converting enzyme 2. Pediatr Res. 2011;71:13–9.
13. Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci. 2020b;12:8. https://doi.org/10.1038/s41368-020-0074-x.
14. Yang N, Shen H. Targeting the endocytic pathway and autophagy process as a novel therapeutic strategy in COVID-19. Int J Biol Sci. 2020a;16:1724–31.
15. Hu T, Frieman M, Wolfram J. Insights from nanomedicine into chloroquine efficacy against COVID-19. Nat Nanotechnol. 2020;15:247–9.
16. Li C, Wang X, Wang H. Repurposing host-based therapeutics to control coronavirus and influenza virus. Drug Discov Today. 2019;24:726–36.
17. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181(2):271–280.e8.
18. Massimino M, Stella S, Tirrò E, Pennisi M, Vitale S, Puma A, et al. ABL1- directed inhibitors for CML: efficacy, resistance and future perspectives anticancer research. 2020;40(5):2457–65.