DOI: 10.1002/jmv.26461

LETTER TO THE EDITOR

JOURNAL OF MEDICAL VIROLOGY WILEY

Targeting NLRP3 inflammasome in an animal model for Coronavirus Disease 2019 (COVID-19) caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

Dear Editor,

We read with interest the contribution of Lucchesi et al on the clinical and biological data on the use of hydroxychloroquine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) supporting the role of the NLRP3 inflammasome in the pathogenesis of the respiratory disease.[1] There is enough evidence that the NRLP3 inflammasome is activated in SARS-CoV-2 infection.[2] Acute respiratory distress syndrome with systemic inflammation has a tremendous lung injury, which is associated with the release of inflammatory cytokines interleukin-6 (IL-6) and IL-1β, and a similar cytokine storm is seen in severe SARS-CoV-2 infection.[3,4] There is a dysregulated proinflammatory cytokine cascade triggered by an intense, rapid activation of the innate immune response, and aberrant IL-6 is incredibly predictive of coronavirus disease 2109 (COVID-19) fatality, as evidenced in post mortem evaluation of patients with COVID-19.[5] Although the inflammatory basis underlying COVID-19 fatality renders the development of immunoregulatory agents of paramount importance, there is no animal model in which some therapeutics can be used. In consideration of the sagacity expressed by the group of Lucchesi et al,[1] we suggest that an animal model based on NLRP3 inflammasome may be helpful. We are familiar with this animal model because it can be used for studying inflammatory bowel disease.[6,7] *Citrobacter rodentium* is a noninvasive Gram-negative bacterium, which is a natural mouse pathogen, commonly used for the study of enteric infections and bacteria-induced inflammation as it resembles enteropathogenic and enterohaemorrhagic *Escherichia coli* infections in humans.[6,7] Transmembrane Toll-like receptors-2 (TLR-2) and TLR-4, the signaling adapter protein myeloid differentiation factor (MyD)-88, and nuclear factor-κB mediate the inflammatory response to *C. rodentium* by recruiting macrophages and neutrophils through the induction of chemokines. The same chemokines are also playing an essential role in the autophagy-inflammasome interplay of heart failure.[8]

Interestingly, with patients COVID-19 may also show diarrhea and gastrointestinal symptoms that may resemble an inflammatory bowel disease in some patients.[9,10] In mice, the oral bacterial transmission by *C. rodentium* starts with the passage through the cecum and subsequent colonization of the colonic epithelium and determining lesions, including the destruction of brush-border microvilli, goblet cell depletion, epithelial cell hyperplasia. According to the genetic background and age of the mouse, the outcome can range from self-limited colitis to fatality with an aggressive adaptive immune response for 2 to 4 weeks. The intestinal homeostasis and epithelial integrity are intimately regulated by other molecules, including the cytosolic nucleotide-binding oligomerization domain (NOD) and the NOD-like receptor (NLR) family expressed in both macrophages and epithelial cells. Mice lacking NOD1 or NOD2 are impaired in *C. rodentium* clearance with classical signs of inflammation and dissemination.[11] The macrophage NLRP3 protein has been demonstrated to be a key component in the immune response to *C. rodentium*.[6,12] However, it remains unclear how *C. rodentium* activates NLRP3 inflammasome. It triggers procaspase-1 dimerization and self-activation, which then processes the maturation of cellular IL pro-IL-1b, and pro-IL-18 to the active cytokines, leading to their secretion by an undetermined pathway. Interestingly, *C. rodentium* can also induce caspase-1-dependent IL-1b maturation and flow through a synergistic TLR-4 and NLRP3 path in vivo.[6] Mice lacking the Nlrp3 gene are more susceptible to induced experimental inflammatory bowel disease, and Nlrp32/2 macrophages did not respond to pathogen-associated microbial patterns. Alipour et al previously demonstrated that compensation of IL-1b in mice lacking the NLRP3 inflammasome might promote the clearance of *C. rodentium* by stimulating inflammatory macrophages in the early stages of infection. On the other hand, IL-1b overcompensation may be disadvantageous in wild type mice.[6] Thus, we strongly suggest that this animal model may be used to test SARS-CoV-2 countermeasures accurately.

Consolato M. Sergi[1]
Brian Chiu[2]
[1]*Department of Pediatrics, Stollery Children's Hospital, University of Alberta, Edmonton, Alberta, Canada*
[2]*Laboratory Medicine and Pathology, University of Alberta, Edmonton, Alberta, Canada*

Correspondence
Consolato Sergi, Department of Laboratory Medicine and Pathology, University of Alberta, 8440 112 St, NW, Edmonton, AB T6G 2B7, Canada.
Email: sergi@ualberta.ca

ORCID

Consolato M. Sergi http://orcid.org/0000-0002-2779-7879

REFERENCES

1. Lucchesi A, Silimbani P, Musuraca G, et al. Clinical and biological data on the use of hydroxychloroquine against SARS-CoV-2 could support the role of the NLRP3 inflammasome in the pathogenesis of respiratory disease. *J Med Virol*. 2020:jmv.26217.
2. Freeman TL, Swartz TH. Targeting the NLRP3 Inflammasome in severe COVID-19. *Front Immunol*. 2020;11:1518.
3. Colantuoni A, Martini R, Caprari P, et al. COVID-19 sepsis and microcirculation dysfunction. *Front Physiol*. 2020;11:747.
4. Coperchini F, Chiovato L, Croce L, Magri F, Rotondi M. The cytokine storm in COVID-19: an overview of the involvement of the chemokine/chemokine-receptor system. *Cytokine Growth Factor Rev*. 2020;53:25-32.
5. He L, Ding Y, Zhang Q, et al. Expression of elevated levels of pro-inflammatory cytokines in SARS-CoV-infected ACE2+ cells in SARS patients: relation to the acute lung injury and pathogenesis of SARS. *J Pathol*. 2006;210(3):288-297.
6. Alipour M, Lou Y, Zimmerman D, et al. A balanced IL-1beta activity is required for host response to Citrobacter rodentium infection. *PLoS One*. 2013;8(12):e80656.
7. Alipour M, Zaidi D, Valcheva R, et al. Mucosal barrier depletion and loss of bacterial diversity are primary abnormalities in paediatric ulcerative colitis. *J Crohns Colitis*. 2016;10(4):462-471.
8. Chiu B, Jantuan E, Shen F, Chiu B, Sergi C. Autophagy-inflammasome interplay in heart failure: a systematic review on basics, pathways, and therapeutic perspectives. *Ann Clin Lab Sci*. 2017;47(3):243-252.
9. Ahlawat S, Asha, Sharma KK. Immunological co-ordination between gut and lungs in SARS-CoV-2 infection. *Virus Res*. 2020;286:198103.
10. Cha MH, Regueiro M, Sandhu DS. Gastrointestinal and hepatic manifestations of COVID-19: a comprehensive review. *World J Gastroenterol*. 2020;26(19):2323-2332.
11. Geddes K, Rubino SJ, Magalhaes JG, et al. Identification of an innate T helper type 17 response to intestinal bacterial pathogens. *Nat Med*. 2011;17(7):837-844.
12. Liu Z, Zaki MH, Vogel P, et al. Role of inflammasomes in host defense against Citrobacter rodentium infection. *J Biol Chem*. 2012;287(20):16955-16964.