LETTER TO THE EDITORS

# Why the immune system fails to mount an adaptive immune response to a COVID-19 infection

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Dear Editors,

The COVID-19 pandemic has already affected many thousands of people and has become the greatest health challenge worldwide [1]. The range of clinical presentations varies from asymptomatic and mild clinical symptoms to acute respiratory-distress syndrome (ARDS) and death. Due to the unknown number of asymptomatic viral-shedding and pauci-symptomatic people in the community, the total number of infections is uncertain. As yet, effective treatment is unavailable. However, the results of preliminary studies and clinical trials are improving our understanding of the pathogenesis and treatment of COVID-19. Herein, we share our personal opinions on the immunopathogenesis of this infection. The virus enters the cell via the angiotensin-converting enzyme-2 (ACE-2) and is sensed (essentially) by Toll-like receptor 7 (TLR7), which exists in endosomes [2]. TLR7 activation leads to the production of alpha interferon, TNF-alpha, and the secretion of interleukin (IL)-12 and IL-6. This results in the formation of $CD8^+$-specific cytotoxic T cells and, through the $CD4^+$ helper T cell, leads to the formation of antigen-specific B cells and antibody production [3,4]. This adaptive immune response controls the viral infection and determines clinical recovery.

It seems that when the body is unable to produce an adequate adaptive response against the virus, the persistent innate-induced inflammation can then lead to a cytokine storm, ARDS, and diffuse organ involvement [5]. Apart from importance of comorbidities like hypertension, diabetes mellitus, and coronary heart disease in increasing the risk of mortality, immunosenescence must play a crucial role. With aging, the population of naïve T cells shrinks while antigen-experienced, memory T cells comprise an important portion of T-cells population [6,7]. It means that the ability of immune system of elderly to respond to previously exposed pathogens is more preserved compared to never-exposed pathogens. In contrast, in children there is huge number of naïve T cells ready to be educated by new pathogens. This can be one of the explanations for COVID-19 milder presentation and significantly lower mortality in children compared to elderly. This situation is close to solid organ-transplanted (SOT) patients because our routine immunosuppressive drugs are effective against naive T cells but not able to block memory T-/B cells.

During TLR7 signaling-related cytokine secretion, IL-6 may play an important role. Interleukin-6 has a pleotropic role across the immune system. It is crucial in the formation of follicular helper T cells, TH17 subset deviation, and for the formation of long-lived plasma cells. However, IL-6 can block $CD8^+$ cytotoxic T cells by inhibiting the secretion of gamma interferon. Moreover, IL-6 by inducing suppression of cytokine signaling (SOCS-3) and increasing the expression of PD-1 can paralyze the cell-mediated antiviral response during a cytokine storm [8]. Among the current medications used to manage COVID-19, although results from the antiviral drugs are still inconclusive [9], studies on chloroquine and its less toxic derivative hydroxychloroquine have been associated with shortening viral replication [10]. Their mechanisms of action are to block viral replication in the endosome by preventing endosomal acidification and endolysosomal fusion. Moreover, hydroxychloroquine blocks entry of the virus into cells. In addition, hydroxychloroquine can block TLR7 and TLR9 signaling and, thus, can reconstruct the $CD8^+$ cytotoxic viral response [11,12]. The addition of azithromycin further reduces the nasopharyngeal COVID-19 virus PCR, as shown by Gautret *et al.* [13]. This is probably through azithromycin immunomodulatory activity via blocking IL-6 and TNF-alpha.

Furthermore, in severe COVID-19 cases, for example, in ARDS, a preliminary report from China showed that


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the addition of tocilizumab was efficient via blocking IL-6 activity [14]. A clinical trial in Italy (TOCIVID-19) is ongoing (NCT04317092).

Data are still very limited regarding the optimal management of transplant patients. Some centers [15-18] aggressively reduce the immunosuppression by withdrawing antimetabolites, discontinue or major reduction in calcineurin inhibitor (CNI) while keeping small doses of steroids. Attention must also be paid to the major interaction between protease inhibitors (lopinavir–ritonavir) and CNIs. Moreover, it seems necessary to reduce the dose of CNIs while using chloroquine or hydroxychloroquine. Frequent monitoring of CNI drug levels is recommended. However, Carbajo-Lozoya *et al.* have shown that Coronavirus (CoV) replication depends on active immunophilin pathways. Tacrolimus can strongly inhibit the growth of the human coronaviruses SARS-CoV, HCoV-NL63, and HCoV-229E at low, noncytotoxic concentrations in cell culture [19]. Based on these data, it makes sense to study the effect of keeping low doses of tacrolimus in COVID-19-infected SOT patients. In more advanced stages of COVID-19 (cytokine storm syndrome), treatment probably should focus on reducing uncontrolled inflammation by blocking IL-6, TNF-alpha, or by removing cytokines by hemoperfusion.

To conclude, in populations at risk (elderly, associated comorbidities, immunosuppressed), when activation of the innate immune system fails to produce an adequate adaptive response (i.e., virus-specific $CD8^+$ T cells), it seems that persistent self-induced inflammation can then cause mortality. Thus, mounting an early adaptive immune response may save lives.

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## Conflicts of interest

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## REFERENCES

1. World Health Organization. https://www.who.int/emergencies/diseases/novel-coronavirus-2019. 19 March 2020.
2. Fung SY, Yuen KS, Ye ZW, Chan CP, Jin DY. A tug-of-war between severe acute respiratory syndrome coronavirus 2 and host antiviral defence: lessons from other pathogenic viruses. *Emerg Microbes Infect* 2020; **9**: 558.
3. Jiankun Z, Chandra C. Toll-Like receptor signaling pathways—therapeutic opportunities. *Mediators Inflamm* 2010; **2010**: 1–7.
4. Zhou Y, He C, Wang L, Ge B. Post-translational regulation of antiviral innate signaling. *Eur J Immunol* 2017; **47**: 1414.
5. Teijaro JR, Walsh KB, Rice S, Rosen H, Oldstone MB. Mapping the innate signaling cascade essential for cytokine storm during influenza virus infection. *Proc Natl Acad Sci USA* 2014; **111**: 3799.
6. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. *JAMA* 2020. https://doi.org/10.1001/jama.2020.4683
7. Weiskopf D, Weinberger B, Grubeck-Loebenstein B. The aging of the immune system. *Transplant Int* 2009; **22**: 1041.
8. Velazquez-Salinas L, Verdugo-Rodriguez A, Rodriguez LL, Borca MV. The role of interleukin 6 during viral infections. *Front Microbiol* 2019; **10**: 1057.
9. Cao B, Wang Y, Wen D, *et al.* A trial of Lopinavir–Ritonavir in adults hospitalized with severe COVID-19. *N Engl J Med* 2020. https://doi.org/10.1056/NEJMoa2001282
10. Gautret P, Lagier JC, Parola P, *et al.* Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-labeled non-randomized clinical trial. *Int J Antimicrob Agents* 2020; 105949.
11. Devaux CA, Rolain JM, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? *Int J Antimicrob Agents* 2020; 105938. https://doi.org/10.1016/j.ijantimicag.2020.105938
12. Zhou D, Dai SM, Tong Q. COVID-19: a recommendation to examine the effect of hydroxychloroquine in preventing infection and progression. *J Antimicrob Chemother* 2020; dkaa114. https://doi.org/10.1093/jac/dkaa114
13. Schultz MJ. Macrolide activities beyond their antimicrobial effects: macrolides in diffuse panbronchiolitis and cystic fibrosis. *J Antimicrob Chemother* 2004; **54**: 21.
14. Xu X, Han M, Li T, *et al.* Effective treatment of severe COVID-19 patients with Tocilizumab. *chinaXiv* 202003.00026v1.
15. Alberici F, Delbarba E, Manenti C, *et al.* Management of patients on dialysis and with kidney transplant during COVID-19 coronavirus infection. https://www.era-edta.org/en/wp-content/uploads/2020/03/COVID
16. López-Oliva MO, González E, Miranda RJ, Jiménez C. Management of kidney transplant immunosuppression in positive coronavirus infection requiring hospital admission. https://www.era-edta.org
17. Zhu L, Xu X, Ma K, *et al.* Successful recovery of COVID-19 pneumonia in a renal transplant recipient with long-term immunosuppression. *Am J Transplant* 2020. https://doi.org/10.1111/ajt.15869
18. Guillen E, Pineiro GJ, Revuelta I, *et al.* Case report of COVID-19 in a kidney transplant recipient: does immunosuppression alter the clinical presentation? *Am J Transplant* 2020. https://doi.org/10.1111/ajt.15874
19. Carbajo-Lozoya J, Müller MA, Kallies S, Thiel V, Drosten C, von Brunn A. Replication of human coronaviruses SARS-CoV, HCoV-NL63 and HCoV-229E is inhibited by the drug FK506. *Virus Res* 2012; **165**: 112.