Hypertension and SARS-Cov-2 infection: is inflammation the missing link?

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The dramatic emergence of the pandemic coronavirus disease COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) raised significant medical and public health concerns for the high disease mortality rate ranging from 1% to more than 5%. In this setting, patients with severe disease exhibit high serum levels of pro-inflammatory cytokines, including interleukin (IL)-1β and IL-6, and their elevated concentrations closely relates to worse outcome.[1] In addition to respiratory failure, cardiovascular system involvement and myocardial damage are associated with a significant increase of mortality rate in infected patients.[2] In fact, pre-existing cardiovascular comorbidities, including hypertension (HTN), diabetes mellitus, cerebrovascular and coronary heart disease, enhance susceptibility to SARS-CoV-2 infection and are associated with increased risk of severe disease, myocardial injury and short-term mortality rate.[3] In particular, HTN emerged as the most common comorbidity among patients with COVID-19 and hypertensive patients display more than three-fold higher mortality risk in comparison to normotensive.[4] However, due to the high prevalence of hypertension in the general population, concerns raised as to whether hypertension represents merely a concomitant risk factor or a pivotal pathogenic trigger of cardiac injury in patients with SARS-CoV2 infection. As reported by Kreutz *et al* in their interesting review article, the identification of angiotensin-converting enzyme 2 (ACE2), highly expressed in cardiac and pulmonary tissue, as a functional receptor for the spike SARS-CoV-2 glycoprotein, focalized considerable attention around the pathophysiologic and clinical consequences of ACE2 upregulation in hypertensive patients with COVID-19 infection.[5] However, as reported, concomitant mechanisms related to inflammatory dysregulation may be advocated to take part in this process.[5] Indeed, the contribution of aberrant innate immune system activation and consequent downstream signalling cascade leading to pro-inflammatory cytokine release has been recognized in various experimental models of HTN.[6] In particular, persistent activation of toll-like receptor (TLR) 4 signalling pathway by different hypertensive stimuli and endogenous damage-associated molecular patterns (DAMPs) emerged as a pivotal immunopathogenic mechanism underlying HTN.[6] Interestingly, TLR 4 has been localized in multiple sites including vessel wall

and alveolar macrophage of severe acute respiratory syndrome mice models. Interestingly, in alveolar macrophage, viral pathogen-associated MP (PAMP) activation of TLR4 signalling may induce oxidative stress and subsequent development of acute lung injury.[7] In particular, activation of macrophage TLR4 leads to induction of two distinct intracellular signalling pathways (MyD88 and TRIF) and rapid cytokine production. In this setting, it may be hypothesized that COVID-19-associated PAMPs may act as exogenous triggers of TLR4 signalling pathway leading to inflammasome activation and inflammatory cytokine release, including interleukin-1β (Figure).[8] We believe that this common activation of innate immune mechanisms may, at least in part, explain the dramatic systemic inflammatory response associated with worse outcome in COVID-19 hypertensive patients.

Conflict of interest: The Authors declare no conflicts of interest.

Funding: No fundings to declare.

References

1. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJl. COVID-19: Consider cytokine storm syndromes and immunosuppression. *Lancet* 2020;**395**:1033-1034.
2. Zheng YY, Ma YT, Zhang JY, Xie, X. COVID-19 and the cardiovascular system. *Nat Rev Cardiol* 2020;**17**:259-260.
3. Guzik TJ, Mohiddin SA, Dimarco A, Patel V, Savvatis K, Marelli-Berg FM, Madhur MS, Tomaszewski M, Maffia P, D'Acquisto F, Nicklin SA, Marian AJ, Nosalski R, Murray EC, Guzik B, Berry C, Touyz RM, Kreutz R, Wang DW, Bhella D, Sagliocco O, Crea F, Thomson EC, McInnes IB. COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options. *Cardiovasc Res* 2020;**116**:1666-1687.

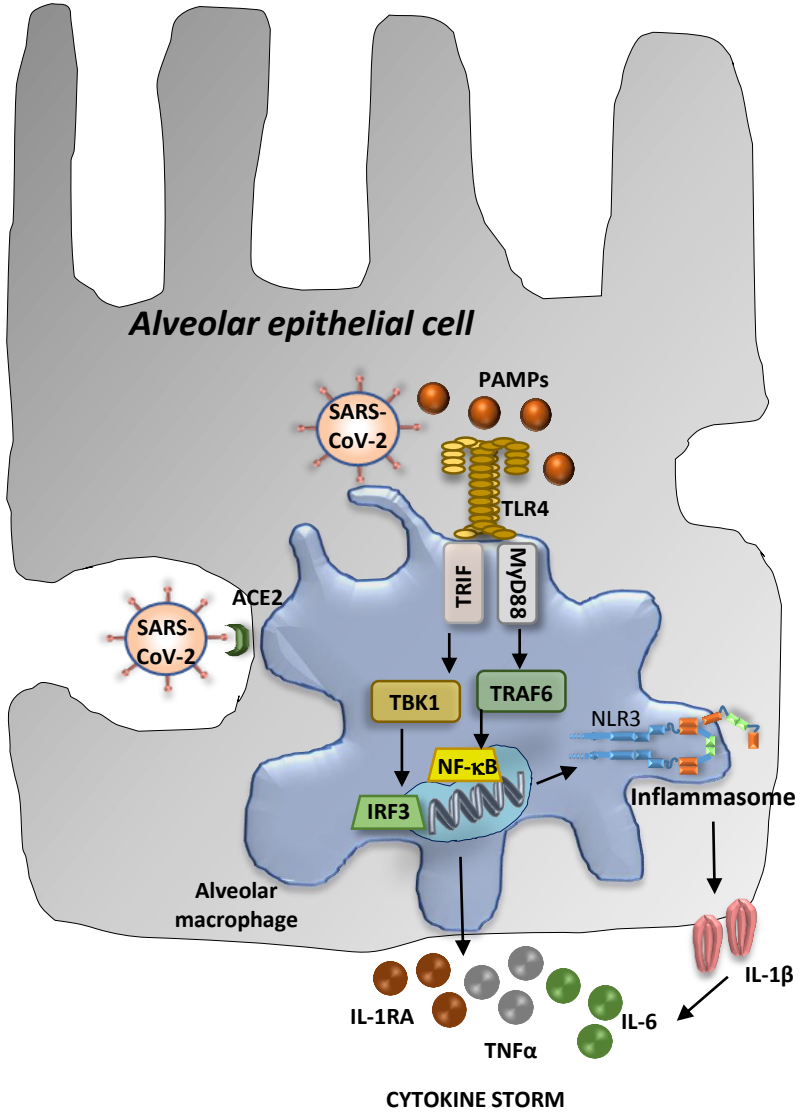
4. Zuin M, Rigatelli G, Zuliani G, Rigatelli A, Mazza A, Roncon L. Arterial hypertension and risk of death in patients with COVID-19 infection: Systematic review and meta-analysis. *J Infect* 2020;**81**:e84-86.
5. Kreutz R, Algharably EAE, Azizi M, Dobrowolski P, Guzik T, Januszewicz A, Persu A, Prejbisz A, Riemer TG, Wang JG, Burnier M. Hypertension, the renin-angiotensin system, and the risk of lower respiratory tract infections and lung injury: implications for COVID-19. *Cardiovasc Res* 2020;**116**:1688-1699.
6. Bartoloni E, Alunno A, Gerli R. Hypertension as a cardiovascular risk factor in autoimmune rheumatic diseases. *Nat Rev Cardiol* 2018;**15**:33-44.
7. Imai Y, Kuba K, Neely GG, Yaghubian-Malhami R, Perkmann T, van Loo G, Ermolaeva M, Veldhuizen R, Leung YH, Wang H, Liu H, Sun Y, Pasparakis M, Kopf M, Mech C, Bavari S, Peiris JS, Slutsky AS, Akira S, Hultqvist M, Holmdahl R, Nicholls J, Jiang C, Binder CJ, Penninger JM. Identification of oxidative stress and Toll-like Receptor 4 signalling as a key pathway of acute lung injury. *Cell* 2008;**133**:235-49.
8. Conti P, Ronconi G, Caraffa A, Gallenga CE, Ross R, Frydas I, Kritas SK. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): Anti-inflammatory strategies. *J Biol Homeost Agents* 2020;**34**:327-331.

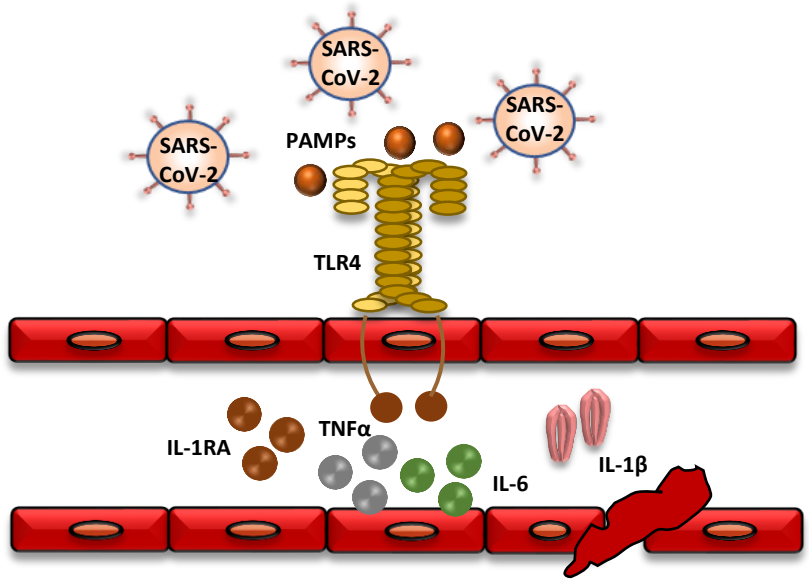
Figure 1 Legend

Alveolar epithelial cell internalize SARS-CoV-2 by angiotensin-converting enzyme 2 (ACE2). Viral PAMPs bind to TLR4 located on alveolar macrophage and activate adaptor protein MyD88-TNF receptor associated factor (TRAF) 6 pathway, nuclear factor kappa B (NF-κB) translocation into the nucleus and proinflammatory cytokine release. TLR4-associated activation of TIR-domain-containing adapter-inducing interferon-β (TRIF) signaling results in a

cascade similar to MyD88 pathway. Moreover, the NLRP3 inflammasome complex may be directly activated by NF-κB with IL-1β secretion and cytokine storm. The same mechanism may occur on endothelial cells inducing endothelial damage and subsequent hypertension.

Figure


Alveolar epithelial cell
PAMPs
SARS-CoV-2
TLR4
TRIF
MyD88
ACE2
SARS-CoV-2
TBK1
TRAF6
NLR3
NF-κB
IRF3
Inflammasome
Alveolar macrophage
IL-1β
IL-1RA
IL-6
TNFα
CYTOKINE STORM


SARS-CoV-2
SARS-CoV-2
SARS-CoV-2
PAMPs
TLR4
IL-1RA
TNFα
IL-6
IL-1β