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Letter

TO THE EDITOR

Precision Medicine in COVID-19: IL-1β a Potential Target

As of April 4, 2020, coronavirus disease-2019 (COVID-19) has been confirmed in 1,395,136 people worldwide, with a mortality of approximately 5.8%.

Since the COVID-19 outbreak, there has been an urgent need for effective treatments. A wide spectrum of disease severity has been described, ranging from asymptomatic, to mildly symptomatic, to severe symptomatic requiring hospitalization, to respiratory failure from acute respiratory distress syndrome. Furthermore, it has been widely reported that the prevalence of the disease is almost 3 times higher in male patients. Overall, this evidence suggests that the prognosis appears to be more conditioned by the host's response than by the infection itself; thus, a precision medicine approach is highly desirable.

Inflammatory responses and the entity of the cytokine storm produced by the infection seem to be variables potentially related to this huge clinical variability. In this view, a multicenter trial on tocilizumab, TOCIVID-19 (Tocilizumab in COVID-19 Pneumonia), a monoclonal antibody that competitively inhibits the binding of interleukin (IL)-6 to its receptor (IL-6R), is ongoing on patients with COVID-19 with pneumonia. To our knowledge, there are no ongoing studies on the inhibition of IL-1.

Evidence suggests that COVID-19 may have originated in bats. Bats, the only flying mammals, have the ability to asymptomatically host a large number of high-profile viruses, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome coronaviruses. It has been reported that fruit bats can be infected with bat SARS coronavirus without showing any sign of infection (1).

In the pre-COVID-19 era, Ahn et al. (2) demonstrated that the ability of bats to tolerate viral disease, even during a transient phase of high viral load, could be explained by a dampened NLR family pyrin domain containing 3 (NLRP3)-mediated inflammatory response. This supports the hypothesis that an enhanced innate immune tolerance rather than an enhanced antiviral defense can be the key point explaining different clinical scenarios in COVID-19. NLRP3 is a critical component of the innate immune system that detects a broad range of microbial motifs, endogenous danger signals, and environmental irritants, mediating caspase 1 activation and secretion of proinflammatory cytokines IL-1β/IL-18 in response to microbial infection and cellular damage (3).

Aberrant activation of the NLRP3 inflammasome is involved in the pathophysiology of various diseases including diabetes, atherosclerosis, and metabolic syndrome, all of which have been shown to be comorbidities associated with worse outcome in COVID-19. In this regard, canakinumab, a therapeutic monoclonal antibody targeting IL-1β, significantly lowers the rate of recurrent cardiovascular events in patients with a previous of myocardial infarction. In cardiovascular diseases, an important source of inflammatory mediators, including IL-1β, is the visceral adipose tissue (4). Of note, activation of NLRP3 inflammasome in macrophages attenuates uncoupling protein 1 (UCP1) induction and mitochondrial respiration in cultures of primary adipocytes, and the NLRP3 inflammasome activation appears to link obesity and dysfunctional thermogenesis (5).

In conclusion, there are many open questions that merit exploration: 1) verifying the role of NLRP3 in the clinical variability of COVID-19; 2) testing the potential therapeutic effect in COVID-19 of IL-1β inhibition (canakinumab, anakinra); and 3) exploring the role of visceral adipose tissue in the inflammatory response to SARS-COV-2 infection.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For

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REFERENCES

1. Watanabe S, Masangkay JS, Nagata N, et al. Bat coronaviruses and experimental infection of bats, the Philippines. Emerg Infect Dis 2010;16:1217–23.

2. Ahn M, Anderson DE, Zhang Q, Tan CW, Lim BL, et al. Dampened NLRP3-mediated inflammation in bats and implications for a special viral reservoir host. Nat Microbiol 2019;4:789–99.

3. Sutterwala FS, Haasken S, Cassel SL. Mechanism of NLRP3 inflammasome activation. Ann N Y Acad Sci 2014;1319:82–95.

4. Parisi V, Petraglia L, Cabaro S, et al. Imbalance between interleukin-1β and interleukin-1 receptor antagonist in epicardial adipose tissue is associated with non ST-segment elevation acute coronary syndrome. Front Physiol 2020;11:42.

5. Okla M, Zaher W, Alfayez M, Chung S. Inhibitory effects of toll-like receptor 4, NLRP3 inflammasome, and interleukin-1β on white adipocyte browning. Inflammation 2018;41:626–42.