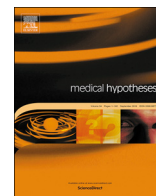




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## Letter to Editors

## Factors involved in low susceptibility to COVID-19: An adaptation of high altitude inhabitants



Dear Editor,

Coronavirus disease 2019 (COVID-19) has caused almost ten million confirmed cases and almost 500 thousand deaths worldwide as of June 25, 2020. SARS-CoV-2 uses Angiotensin-converting enzyme (ACE)-2 receptors to enter human cells. These receptors thus perform a vital role in the progression and prognosis of the disease. A high expression of ACE-2 receptors in type II apical surface epithelial cells makes the lungs the main target organs of the infection. This increases the possibility of complications such as pneumonia, acute distress syndrome and death.

On the other hand, Zhou et al. associate Interleukin (IL) 6 and ferritin with the fatal outcome of infected patients [1]. Moreover, it is known that many patients in intensive care units have high levels of IL1, IL2, IL6, IL7, IL10 and IL18 [2,3]. IL1, IL6, and IL10 regulate intracellular iron content by modulating transferrin receptors, as well as ferritin and hepcidin expression [4]. As a result, available iron varies, affecting oxygen uptake and transport. This might explain why inhabitants of high altitude areas (+2500 m above sea-level) might be affected by SARS-CoV-2 to a lesser extent because their respiratory, circulatory, and hematological systems are adapted to stress conditions such as hypobaric hypoxia. Arias-Reyes et al. [5] reported that people living in high altitude areas are less susceptible to developing severe symptoms of COVID-19.

Therefore, what factors are involved in making this population less susceptible to developing severe-pathological conditions in case of a SARS-CoV-2 infection? Our hypothesis is that there are three factors involved in the lower susceptibility in these populations:

- Variable expression of ACE-2 receptors: People living in high altitude areas would have lower expression of ACE-2 receptors [5]. Consequently, these populations would have less susceptibility to SARS-CoV-2, because it would be more difficult for the virus to enter cells, and thus even infected people would be much less likely to develop severe pathological conditions of COVID-19.
- Hypoxia inducible factor regulation: High altitude inhabitants have the hypoxia-inducible factor activated, leading to a subsequent gene overexpression on erythropoietin-erythropoiesis production [6]. In addition, this signaling pathway decreases ACE-2 expression [7]. Consequently, populations from high altitude areas would be less susceptible to hypoxia during the infection.
- Pulmonary adaptation in high-altitude areas: Low partial pressure of oxygen in the environment and lower inspired partial pressure of oxygen leads to pulmonary physiological and anatomical adaptations [8], improving the pulmonary perfusion and capacity. Consequently, SARS-CoV-2 infected populations from high altitude areas

have greater lung adaptive capacity than those that live at low altitude.

The three factors above would perform an important role in high altitude inhabitants, because they decrease the susceptibility to develop severe symptoms in SARS-CoV-2 infection. It is worth mentioning that it is possible to quantify the ACE-2 receptor expression, interleukins and elucidate the molecular mechanisms involved.

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## Conflict of interest statement

The authors declare that there is no conflict of interest.

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Celia Choquenaira-Quispe<sup>a</sup>, Vanessa Saldaña-Bobadilla<sup>b</sup>,  
J. Kenedy Ramirez<sup>c,\*</sup>

<sup>a</sup> Programa de Pós-graduação em Ciências Farmacêuticas, Universidade Federal do Ceará, Fortaleza, Brazil

<sup>b</sup> Departamento de Farmacotecnia, Facultad de Farmacia y Bioquímica, Universidad Nacional de Trujillo, Av. Juan Pablo II s/n, 13011 Trujillo, Peru

<sup>c</sup> Facultad de Farmacia y Bioquímica, Universidad Nacional de Trujillo, Av. Juan Pablo II s/n, 13011 Trujillo, Peru

E-mail address: [jramirezch@unitru.edu.pe](mailto:jramirezch@unitru.edu.pe) (J.K. Ramirez).

\* Corresponding author.