Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Should we unstress SARS-CoV-2 infected cells?

SARS-CoV-2 has caused an unprecedented challenge to the medical and scientific communities around the world. For weeks, we have struggled to figure out why some patients develop a severe symptomatology and die while others are asymptomatic. Correlation studies have associated several medical conditions like lung disease, cardiovascular conditions, diabetes, obesity, kidney and liver disease among others (CDC.org), however, no mechanism of disease has been elucidated to explain such correlations. During the first weeks of the pandemic, inflammation and cytokine storm syndrome were suggested and proved to be part of the mechanism that leads to severe development of the COVID19. Since then, an increasing number of therapeutic strategies against the inflammation and cytokine release have been proposed and investigated: steroids, intravenous immunoglobulins, selective cytokine blockers (eg, anakinra or tocilizumab) and Janus Kinase (JAK) inhibitors (eg, baricitinib), thus, many previously developed cytokine inhibitory drugs are being tested for COVID19. These treatments were initially conceived for inflammatory disease such as rheumatism, intestinal inflammation or psoriasis; people under such treatments have been speculated to be partially protected from severe COVID19 [1]. Those conditions, however, are chronic immune-mediated inflammatory diseases. On the other hand, COVID19 produces an acute inflammatory process that cannot be resolved by individual inhibition of specific cytokines. The alternative, a potent or absolute blockage of cytokine pathway (eg. with JAK blockers), could interfere with the innate immune response necessary to fight the first stages of infections. A possible solution to this impasse could be the use of precision medicine approaches searching for modulation of upstream regulators of the inflammatory response, as modulation would not mean a complete disruption of the inflammatory pathway but only control of the thresholds that lead to over-activation. The one-million-dollar question is: what triggers the hyperinflammatory process during the virus infection? Cellular stress (including Endoplasmic Reticulum (ER) stress, Oxidative Stress and mitochondrial stress) is a group of pathways that connects infection and inflammation [2,3] and a potential candidate for such approach. There are several ways in which viruses can induce cellular stress, but a recent study showed that the SARS-CoV virus, the one responsible for the severe acute respiratory syndrome outbreak in 2002, forms insoluble intracellular aggregates from its Open Reading Frame 8B (ORF8b) inducing ER stress, lysosomal damage and autophagy activation. ORF8b induced cell death in epithelial cells that could be partially rescued by reducing the canonical cause of ER stress (protein aggregation). And in macrophages, ORF8B activated NLRP3 inflammasome [4], connecting SARS-CoV infections and inflammation through cellular stress.

As aging is part of the correlation with COVID19 severity, oxidative stress and its mediator NRF2 have also been proposed to part of the mechanism [5]. NRF2 protects against oxidative stress and declines with age. This lack of NRF2 diminishes the ability to combat infections, prevent cell death and it is associated with an increase of NF-kB signaling and inflammation [6]. Altogether, this evidence suggests that cellular stress could be an important part of the mechanism of disease for severe cases of COVID19 with hyperinflammatory response.

Cellular stress has been a therapeutic target for multiple disorders for several decades. The group of molecules that mitigate the effects of ER stress are called chemical chaperones. One of them, 4-Phenylbutiric acid (4-PBA) has been used since the 80 s to treat urea cycle disorders. It effectively reduces the effects of misfolded and aggregated proteins but more importantly, it reduces the inflammatory response in many conditions related with pulmonary and cardiovascular disease, liver failure, pancreatitis, diabetic encephalopathy, osteoarthritis, osteolysis among others [7–16]. 4-PBA is an approved drug that could be used immediately for patients in the current outbreak. Recently, our group, developed a 4-PBA treatment for lung disease based in the stress mechanism of disease. Mice that die at birth due to respiratory insufficiency caused by mutations in Serpinh1, a collagen chaperone involved in ER stress response, improved their respiratory function and survived to perinatal stages after treatment during pregnancy with 4-PBA (P-585,531). It is necessary to do further research to prove the inflammatory component of this model, but our results suggest that 4-PBA treatment could be used to prevent respiratory failure in COVID19 patients if the ER stress is confirmed to be part of the mechanism. Another possible therapy arises from the modulation of oxidative stress. McCord and colleagues propose PB125, a NRF2 activator, as a strategy to downregulate ACE2 and decrease proinflammatory cytokines [17]. This compound could represent a double strategy to reduce virus replication and the development of the cytokine storm syndrome.

If stress were confirmed as mechanism of COVID19, there is another relevant application that could be used to improve the assistance to COVID19 patients: many medical preconditions associated with risk in COVID19 usually present inflammation and stress [18–22], therefore, this population would be systemically primed with pro-inflammatory signals and promote the development of an hyperinflammatory response when infected with SARS-CoV-2 or other related viruses (see Fig. 1). The positive aspect of this connection is that if previous conditions prime the body with stress signals, these could be used to predict a severe development of the COVID19 in early stages of the disease. The *Binding Immunoglobulin Protein* (BiP) is an ER stress master regulator and is secreted to the circulation under stress conditions. This could be used to test patients at initial stages of the infection to start a prophylactic treatment with a chemical chaperone or anti-inflammatory therapy. Similarly, NRF2, could be used as marker for oxidative stress and risk for COVID19, which would expand the panel of signals that predict severe output of the infection.

Nowadays we know that research in mechanisms of disease and precision therapies are an efficient approach to deal with current medical challenges. If we dig deep into the COVID19 mechanism, we could uncover a significant participation of the stress pathways on inflammation and cytokine storm syndrome associated with bad

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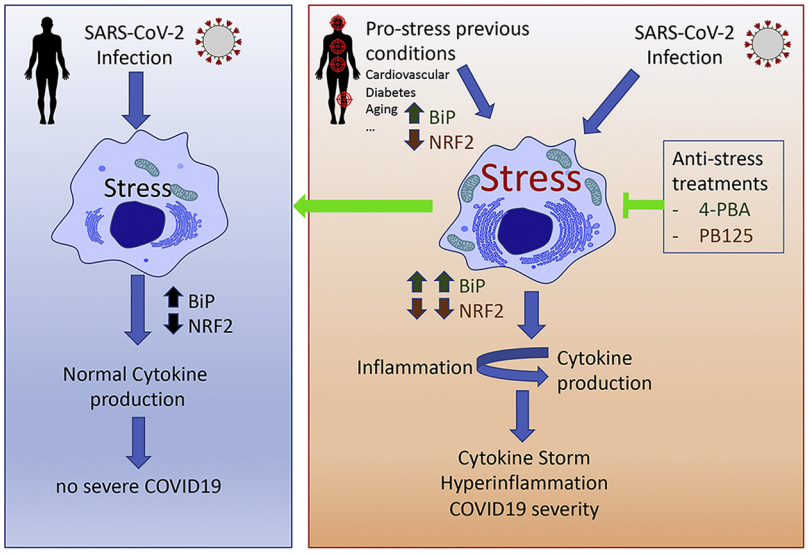

Fig. 1. Celular stress modulates inflamatory signals related to COVID19. A. Infected patients without previous cellular stress related conditions usually respond to SARS-CoV-2 infections through controled cytokine response as asymptomatic or mild COVID19 disease. B. Patients with previous conditions related to celular stress diseases such as diabetes, cardiovascular or certain pro-inflammatory pathologies predispose to a hiperinflammatory process that leads to cytokine storm and severe COVID19 disease.

prognosis in patients infected with SARS-CoV viruses. Thus, we could use this mechanism to predict and mitigate complications in COVID19 improving the outcomes of SARS-CoV-2 infections.

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Ivan Duran I am a cell biologist. My work focus in mechanisms of diseases and precision therapies. I obtained my PhD in the University of Malaga, Spain. I moved to the US for two postdoctoral stays, one at Cornell University and the second one at University of California Los Angeles. During this time, I participated in projects investigating developmental pathologies in several models and systems. Then I obtained a Junior Faculty position at UCLA where I focused in precision medicine approaches and developed new treatments for Bone fragility and respiratory insufficiency based in the cellular stress as a mechanism of disease. I am currently a professor at University of Malaga with a multidisciplinary research group studying mechanistic and therapeutic approaches to human pathology. We use a precision medicine philosophy to understand diseases and generate personalized treatments. Our research areas investigate from basic aspects of disease at the molecular level to translational cutting-edge translational studies in nanomedicine.

Fabiana Csukasi
Department of Orthopaedic Surgery, University of California–Los Angeles, Los Angeles, CA 90095, USA

Gustavo Rico[a,b]
[a] *Department of Cell Biology, Genetics and Physiology, Faculty of Sciences, University of Málaga, IBIMA, Spain*
[b] *Networking Biomedical Research Center in Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN). Andalusian Centre for Nanomedicine and Biotechnology-BIONAND, 29071, Málaga, Spain*

Jose Becerra[a,b]
[a] *Department of Cell Biology, Genetics and Physiology, Faculty of Sciences, University of Málaga, IBIMA, Spain*
[b] *Networking Biomedical Research Center in Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN). Andalusian Centre for Nanomedicine and Biotechnology-BIONAND, 29071, Málaga, Spain*

Ivan Duran[a,b,c,*]

[a] Department of Orthopaedic Surgery, University of California–Los Angeles, Los Angeles, CA 90095, USA

[b] Department of Cell Biology, Genetics and Physiology, Faculty of Sciences, University of Málaga, IBIMA, Spain

[c] Networking Biomedical Research Center in Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN). Andalusian Centre for Nanomedicine and Biotechnology-BIONAND, 29071, Málaga, Spain

E-mail address: ijduran@uma.es.

[*] Corresponding author at: Department of Cell Biology, Genetics and Physiology, Faculty of Sciences, University of Málaga, Severo Ochoa 35, 29590, Malaga, Spain