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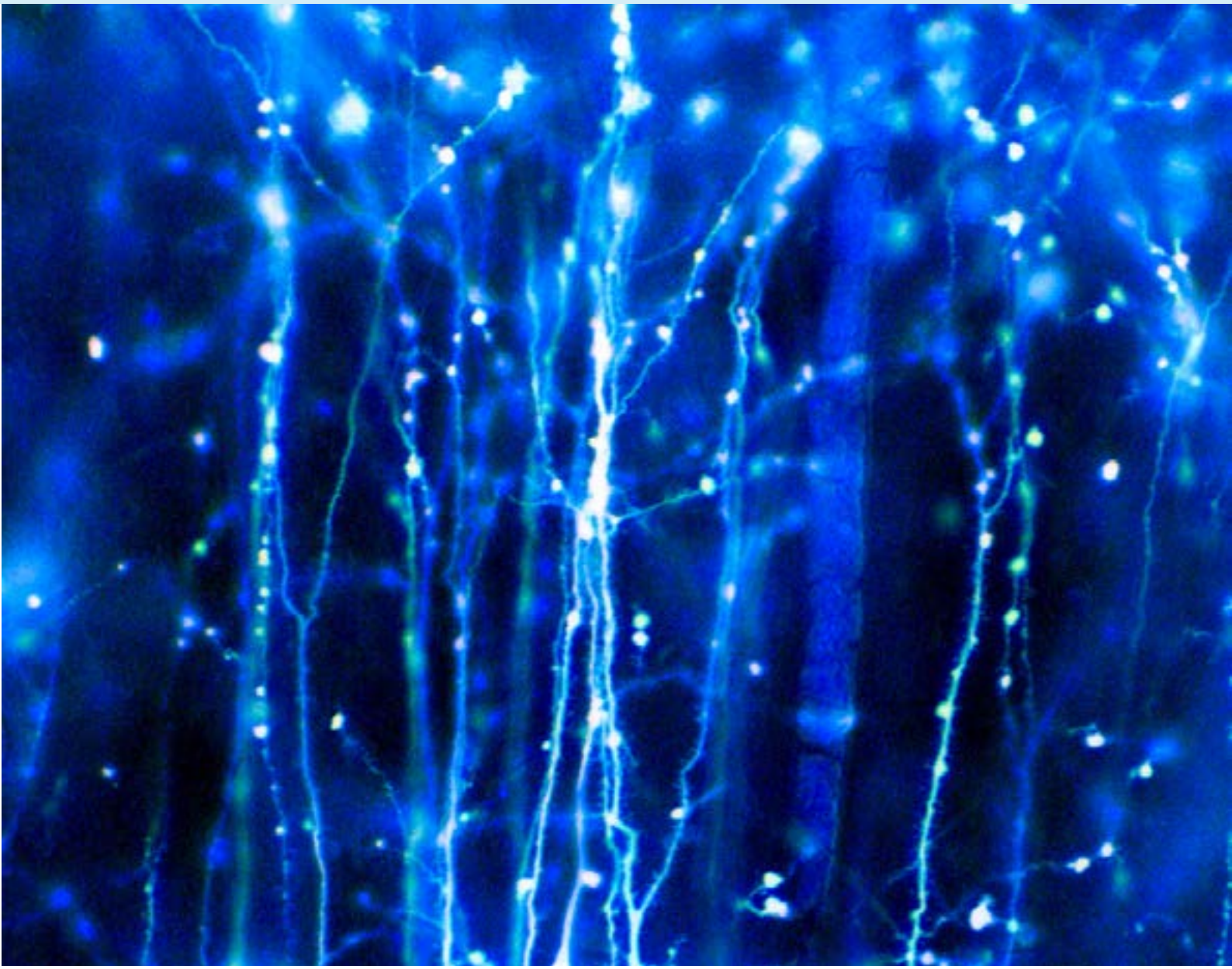

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Special ISSUE

A comment on COVID-19 **Volume 13**

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We would like to share with all the members of our scientific community, this comment on COVID-19, a collaboration of the past president of the Brazilian Physiological Society, María José Campagnole-Santos and her co-woekers.

"ACE2 a double-edged sword?"

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Angiotensin-converting enzyme 2 (ACE2) is the binding protein/receptor used by the new SARS-CoV-2, which causes 2019 coronavirus disease (COVID-19), to enter host cells [1,2]. In 2003, Li and colleagues [3] at the Harvard Medical School, USA had previously described that a protein (spike proteins - S1 domain) da família do coronavirus binds efficiently to ACE2 [3,4]. From binding to ACE2, the virus envelope fuses into the host cell membrane allowing its genetic material entering the cell and replicate, triggering severe respiratory disease, including acute respiratory distress syndrome (ARDS), a devastating lung disease with high mortality rates (3060%).

ACE2, which is expressed in different cells in the body, is a monocarboxypeptidase that hydrolyzes several peptides, especially peptides from the renin-angiotensin system (RAS) [5,6]. The RAS, through the actions of the ACE/ angiotensin (Ang) II/ AT1 receptor axis, is an important regulator of blood pressure and electrolyte balance. However, inappropriate or long-term activation of this axis is involved with the pathophysiology of several diseases, including inflammatory diseases. Today we recognize that ACE2 is a negative regulator of this system, since ACE2 hydrolyzes with high affinity Ang II forming Ang-(1-7). Ang-(1-7) in turn, through binding to its receptor, Mas, induces several beneficial actions, such as antihypertensive, antiinflammatory, anti-proliferative and anti-fibrotic. The RAS counteraregulator axis is thus constituted by ACE2/ Ang-(1-7)/ Mas receptor [7].

The use of ACE2 by SARS-CoV-2 reduces the availability of this enzyme to hydrolyze Ang II, establishing an important imbalance in the RAS, with a reduction in Ang-(1-7) and an increase in Ang II levels, already demonstrated in ACE2 knockout animals. The consequence of this imbalance can be largely related to the worsening of pulmonary inflammation and the progression of respiratory disease.

Studies carried out in our [8-13] and other (14-19) laboratories have shown that treatment with Ang-(1-7) or agonists of the Mas receptor activates an antiinflammatory response in different pathophysiological conditions. More recently, we have also described that Ang-(1-7) trigger pro-resolutive mechanisms in acute and chronic inflammatory processes [11,12]. In the lung, Mas receptor is expressed in the smooth muscle of the epithelium and airways, alveolar cells, vascular smooth muscle cells and endothelium [7,9,10,20]. Mas receptor has also been identified in cells of the immune system, such as dendritic cells, lymphocytes, macrophages, eosinophils, neutrophils and alveolar macrophages, indicating a cellular mechanism for Ang-(1-7) actions in the immune system [7,11,12 , 20].

In lung inflammation models, such as asthma, pulmonary fibrosis, ARDS and pulmonary emphysema, administration of Ang-(1-7) decreased the synthesis of cytokines and chemokines, the migration of inflammatory cells to the lung and improved lung function [7, 8-20]. In addition, treatment with Ang- (1-7) improved arterial oxygenation and reduced collagen deposition in the lungs in murine ARDS models [17,21,22]. These results suggest that the inhibitory effect of Ang-(1-7) in the recruitment of inflammatory cells observed in the acute phase, may be related to the reduction of fibrosis in the later phase. It is interesting

to note that antiinflammatory effects have also been observed after treatments with the ACE inhibitor, captopril and/ or AT1 receptor antagonist, losartan. These effects can also be related to an increase in Ang-(1-7) levels in the lung [18,19]. In another example of chronic lung inflammation, asthma, it has been shown that treatment with Ang-(1-7) reduced the eosinophil count in the lung, reduced the production of inflammatory mediators, decreased the activation of signaling pathways related to production of cytokines, chemokines and survival of inflammatory cells [8,9]. These anti-inflammatory effects were also accompanied by reduced collagen deposition, less mucus production and improved lung function [8,9].

An important step in the immune response is the resolution of the inflammation. Resolution is an active phenomenon that aims to stop inflammation and restore tissue homeostasis. We recently demonstrated that Ang-(1-7) is a pro-resolutive mediator [11,12]. We found that treatment with Ang-(1-7) at the peak of pulmonary eosinophilic inflammation induced apoptosis of eosinophils, inhibited the signaling pathways related to the production of cytokines and the survival of inflammatory cells and reduced molecules related to the maintenance of the Th2 immune response [11]. In addition, Ang-(1-7) reduced the expression of genes involved in the expression of collagen in the lung [11]. We also observed similar results in a model of neutrophilinduced inflammation, arthritis [12]. In this condition, blocking Mas receptor delayed natural resolution, emphasizing that the ACE2/ Ang-(1-7)/ Mas receptor axis plays an important physiological role in resolving inflammation [12]. Similar results were observed in studies of pulmonary inflammation in progress in our laboratory. In addition, in FVBN mice, a strain resistant to the asthma model, genetic deletion of the Mas receptor worsened inflammation and worsened lung remodeling when these animals were subjected to experimental asthma [10]. Therefore, in addition to the therapeutic administration of Ang-(1-7), the results of our group strongly suggest that the absence or malfunction of the ACE2/ Ang-(1-7)/ Mas receptor pathway intensifies the inflammation, affects its resolution and contributes for impaired function of the inflamed tissue.

The harmful role of ACE2 as a mediator of SARS-CoV-2 entry into lung cells is a relevant issue and needs to be studied in detail. Recently, the use of protease inhibitors [23] in order to block ACE2, has been suggested as a therapy for the treatment of COVID-19. However, studies have already shown that the absence of ACE2 (knockout animals, $ACE2^{-/Y}$) resulted in thickening of the alveolar wall, pulmonary congestion and edema, infiltration of inflammatory cells and hyaline membrane in a sepsis model [24]. In addition, intraperitoneal injection of recombinant human ACE2 protein (rhuACE2) in $ACE2^{-/Y}$ mice subjected to ARDS model [24] or overexpression of ACE2 [25] prevented the increase in respiratory system elastance and pulmonary edema [24] and improved pulmonary histopathology, decreased neutrophils and pulmonary inflammatory mediators, reduced Ang II and increased pulmonary levels of Ang- (1-7) [25,26].

In COVID-19, the RAS axis with anti-inflammatory and pro-resolving role is impaired by the binding of SARS-CoV-2 to ACE2. Thus, therapeutic strategies aimed only at inhibiting ACE2 need to be evaluated with caution. Activation of the Mas receptor by Ang-(1-7) or its analogs alone or in combination with the administration of soluble recombinant ACE2 that binds to the virus spike proteins and leaves the ACE2-bound to the cell membrane available [27], can be important additive measures to control the SARS-CoV-2-mediated inflammatory response in the lung.

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