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COMMENTARY

SARS-CoV-2-mediated inflammatory response in lungs: should we look at RAGE?

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In December 2019, a new type of coronavirus pneumonia (COVID-19) emerged in Wuhan, China, and spread rapidly all over the world, forcing the World Health Organization to officially declare on 30 January 2020, the COVID-19 as a global pandemic. Lung inflammation is the main cause of life-threatening respiratory disorders at the COVID-19 severe stage [1, 2].

The etiological agent of this new pandemic is a novel coronavirus, the SARS-CoV2, which uses the angiotensin converting enzyme 2 (ACE2) molecule as the receptor for viral cell entry [3]. ACE2 plays an important role in the renin–angiotensin system (RAS), and the imbalance between ACE/Ang II/AT1R pathway and ACE2/Ang (1–7)/Mas receptor pathway in the RAS system will lead to multisystem inflammation [4].

It is well known that increased ACE and Ang II are poor prognostic factors for severe pneumonia [5]. Conversely, different studies including systematic review and meta-analysis have shown that ACE inhibitors/ARBs have a protective role [6, 7]. Furthermore, inpatient use of ACEI/ARB in hypertensive hospitalized COVID-19 patients has been recently associated with lower risk of all-cause mortality compared with ACEI/ARB non-users [8].

Activation of the angiotensin II receptor type 1 (AT1R) by Ang II leads to the induction of NF-κB [9, 10], and subsequent inflammation through pathways distinct from those mediating classical Gq-induced signaling [11].

The receptor for advanced glycation end-products (RAGE), initially recognized for its ability to bind to Advanced Glycation End-products (AGEs), was subsequently found to be a pattern recognition receptor able to recognize several danger signals, including high mobility group box-1 (HMGB1)/amphoterin, S100/calgranulins, and amyloid-β peptide [12, 13].

At present, this multiligand pattern recognition receptor is considered as a key molecule in the onset and sustainment of the inflammatory response in many clinical entities [14–17]. Furthermore, activation of RAGE causes not only an inflammatory gene expression profile but also a positive feed-forward loop, in which inflammatory stimuli activate NF-κB, which induces RAGE expression, followed by a sustained NF-κB activation [18].

The signaling cascades triggered by RAGE engagement are much more complex and diverse than initially thought, considering that RAGE-binding proteins located in either the cytoplasm and or on the plasma membrane can modulate RAGE-mediated signaling diversity, in addition to the conformational flexibility acquired after the engagement, ranging from homo-dimerization, homo-multimerization and even to hetero-dimerization [19, 20].

Noteworthy, a cognate ligand-independent mechanism for RAGE transactivation has been recently reported to occur following activation of the AT1R, in different cell types [21]. Activation of the AT1R by angiotensin II (Ang II) triggered the transactivation of the cytosolic tail of RAGE and NF-κB-driven proinflammatory gene expression, independent of the liberation of RAGE ligands or the ligand-binding ectodomain of RAGE. Furthermore, the adverse proinflammatory signaling events induced by AT1 receptor activation were attenuated when RAGE was deleted or transactivation of its cytosolic tail was inhibited.

At this point, it is important to highlight that RAGE is expressed at a low basal level in most healthy adult tissues, and its expression is up regulated during pathologic processes. However, pulmonary tissues express remarkably high basal levels of RAGE, where it seem to play a homeostatic physiological role in tissue morphology [22].

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Although RAGE has been defined as a specific marker of AT1 cells, after cell injury [23], RAGE may also be expressed in type 2 alveolar epithelial (AT2) cells [24]. In addition to lung epithelium, RAGE expression has also been noted in many crucial cell types in lung physiology, such as vascular smooth muscle cells [25], airway smooth muscle cells [26], and endothelial cells [27].

Considering the abundance of both AT1R and RAGE expression in lungs, the RAGE transactivation produced by Ang II-mediated AT1R activation can run continuously; while, the virus-mediated imbalance of the ACE/Ang II/AT1R pathway is being produced by the binding of SARS-CoV-2 to ACE-2 molecules, and, thus, limiting its function as a RAS counter-regulator.

This new transactivation mechanism opens new questions, considering that RAGE is a highly polymorphic protein, on the possibility that some polymorphisms can alter these intermolecular protein–protein interactions. Furthermore, Ang II exerts several cytokine-like actions via the AT1R and by transactivation of several growth factor receptors, including EGF, platelet-derived growth factor, and IGF receptors [28, 29]. These conditions may then render a wide range of biological responses, as we are seeing in patients affected by COVID-19, where not all infected patients develop a severe respiratory illness.

Due to the compelling body of evidence supporting a crucial role of RAGE activation in many clinical entities, many efforts have been done to inhibit RAGE signaling, and although a very extensive variety of compounds of the most dissimilar nature has been reported as capable of inhibiting RAGE signaling, only a few have been evaluated in clinical trials [30]. Due to the magnitude of this pandemic and its associated costs, and considering that lung injury with severe respiratory failure is the leading cause of death in COVID-19, science cannot afford to rule out any approach to confront this daunting scenario. Although, many vaccine candidates are under development and different anti-RNA viral drugs clinical trials are in course, due to the current urgency to stop the pandemic, it is important to highlight that the more the knowledge generated about inflammatory bronchoalveolar pathophysiology of this disease, the greater the success of the rational design and/or the use of drugs for its treatment.

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