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Influence of aging on T cell response and renin-angiotensin system imbalance during SARS-CoV-2 infection

The viral clearance and the long-term antiviral immunity require an adequate T cell-mediated adaptive immune response. Paradoxically, they can also contribute to the cytokine storm observed in COVID-19 patients [1–3]. The cytokine storm during COVID-19 induces Th17 response promoting vascular permeability [4]. Additionally, Th1, NK, NKT, and CD8 + T lymphocytes along with other innate immune cells that target virus-infected cells may be overstimulated producing tissue damage [5]. Activated T lymphocytes express increased levels of inhibitory immune checkpoints TIM-3, CTLA-4, PD-1, and TIGIT [6]. The persistence of stimulation induces the expression of the inhibitory immune checkpoint sustained in the time with the progressive loss of T lymphocyte effector function, or exhaustion [7,8]. Studies performed in SARS-CoV-2 infected patients revealed the presence in the bloodstream of higher quantities of activated CD4+HLADR + CD38+ T cells and CD4+PD-1+CD57+ exhausted or senescent T cells with respect to healthy controls [9]. Accordingly, patients with severe COVID-19 have CD4 + T cells that express lower levels of IFN-γ, TNF-α, and IL-2 than mild patients, or healthy controls [10]; and CD8 + T cells with high levels of CTLA-4, PD-1, TIGIT, granzyme B, and perforin were found in patients severely ill compared the mild group [10].

Older individuals are more predisposed to suffer infectious diseases. In effect, up to one-third of deaths in aging is a consequence of infectious diseases [11]. The persistence of viral infections throughout life can trigger monoclonal expansion of T cells resulting in low memory T cell variability that can lead to immune exhaustion [12]. This is a problem besides new infectious agents like SARS-CoV-2. Elevated levels of inflammation are characteristic of severe cases of COVID-19 can result in pneumonia with a compromise of the integrity and function of lung tissue. Furthermore, these exhausted T cells preferentially secrete pro-inflammatory cytokines such as TNF-α and IFN-γ [12]. These, together with the cytokines secreted by cells of innate immunity, contribute to the mild inflammatory profile seen in elderly individuals [13].

During acute pulmonary infection diseases, the renin-angiotensin system (RAS) participates in the development of ARDS with consequent pulmonary fibrosis [14], a condition frequently observed in COVID-19 patients [15]. Angiotensin converting enzyme (ACE)-2 is the main receptor for SARS-CoV-2 and also a critical link between immune response and inflammation [16]. ACE2 cleaves angiotensin (Ang)II into Ang1-9 and Ang1-7, inactivating AngII [17]. Ang1-7 antagonizes inflammatory responses [18,19]. It is possible that, under physiological conditions, ACE2 inhibits the production of IL-6 induced by AngII, with the consequent reduction of Th17 cells [20,21]. Additionally, AngII induces TGF-β expression [22,23] involved in the differentiation of Th17 cells and lead to the production of massive quantities of proinflammatory cytokines and chemokines [4,24]. It has been reported in COVID-19 associated with ARDS an increment of the highly proinflammatory CCR6+ Th17 subpopulation [25]. As well, the severity of lung injury shows a significant correlation with the amount of IL-17 [26].

The Ang1-7 controls the phosphorylation of extracellular signal-regulated kinase 1/2 (ERK1/2) [27], thus regulating the IL-10 production. This cytokine induces the differentiation of Th0 cells to Th2 type [28] and, additionally acts as anti-inflammatory factor preventing tissue damage [29,30]. Th2 cells modulate the immune responses via the production of anti-inflammatory cytokines such as IL-5, IL-4, IL-9, and IL-13 [31]. During COVID-19 disease the increase in the proinflammatory T cell response correlated with the low circulating plasma levels of Ang1-7 [32]. A recent molecular model of the impact of SARS-CoV-2 infection on RAS predicts a quantitative reduction in ARDS severity in COVID-19 patients, in agreement with the known anti-inflammation and anti-fibrosis nature of Ang1-7 [33].

Previous evidence obtained from SARS-CoV indicates that the infection can down modulate ACE2 expression on cells [14,34–36]. This mechanism may be involved in COVID-19 and explains the multiple organ injury produced through an increased release of chemokines and proinflammatory cytokines with the increase of vascular permeability and consequent neutrophil migration to the lung [37]. It is still controversial the influence of aging on ACE2 expression. The increase in the susceptibility to cardiovascular disease and vascular injury that affects preferentially the elderly individuals could be explaining by the down regulated ACE2 in aging, as was suggested by several studies [38–40]. However, such age-dependent variation in the ACE2 levels can vary according to cell type. Thereby, an ACE2 depletion in the aortas and kidneys of aging female mice was observed. Similarly, this animal model has shown in the lungs the lowest level of ACE2 when compared with that in the heart, brain, and kidneys [41]. Other conditions such as dietary elements such as high potassium intake decreased ACE2 gene expression [42]. Moreover, the host genetic components that define ACE2 variants also influence its expression levels, which may also impact on COVID-19 outcome [43]. Other host-related conditions such as patients with type II diabetes with severe COVID-19 outcome have revealed diminished levels of ACE2 [44]. In contrast, those persons routinely treated with drugs belongs to Angiotensin-converting enzyme inhibitors (ACEi) and/or Angiotensin II type I receptor blockers (ARBs) have noticed a significant increase in ACE2 expression [46].

Although the expression of ACE2 could be biased by gender, no differences in the activity of this enzyme in the lungs have been demonstrated in the murine model [45]. Besides, in rats, the levels of ACE2 were dramatically reduced with aging in both genders, but with significantly higher expression in old female rats than male [40].

ACE2 protein is expressed in various human organs including oral and nasal mucosa, nasopharynx, lung, stomach, small intestine, colon, skin,

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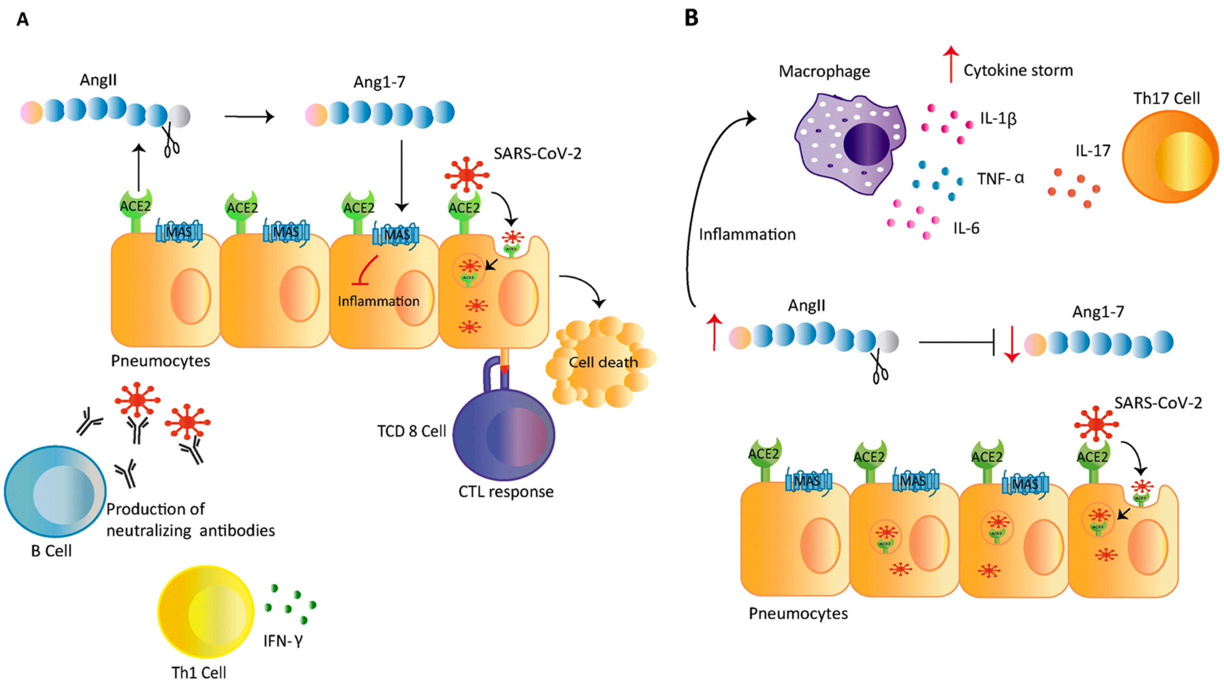

Fig. 1. RAS and T cell response following SARS-CoV-2 infection during controlled (A) and uncontrolled (B) disease.
Angiotensin-converting enzyme 2 (ACE2) cleaves angiotensin II (Ang II) into Ang 1-7, inactivating Ang II. Ang 1-7 via MAS receptor antagonizes inflammatory response allowing an effective Th1 response (A). During acute pulmonary infection diseases, RAS participates in the development of ARDS with consequent pulmonary fibrosis. The unbalance between AngII and Ang 1-7 inducing the differentiation of Th17 cells that secrete numerous cytokines. In particular, IL-17 per se induces the production of massive quantities of proinflammatory cytokines and chemokines (B).

lymph nodes, thymus, bone marrow, spleen, liver, kidney, and brain [47]. There was little to no expression of ACE2 on most of the human peripheral blood-derived immune cells including CD4 + T, CD8 + T, activated CD4+ /CD8 + T, Tregs, Th17, NKT, B, NK cells, monocytes, dendritic cells, and granulocytes. However, it was observed high expressions of ACE2 on human tissue macrophages, such as alveolar macrophages, liver Kupffer cells, and microglial cells in steady state brain [48,49]. Thus, it is relevant to consider potential unfavorable effects of SARS-CoV2 on macrophages, using these cells as a Trojan horse, enabling viral anchoring specifically within the pulmonary parenchyma, which may govern the severity of SARS-CoV-2 infection. Moreover, reallocation of viral-containing macrophages migrating out of the lung to other tissues is theoretically plausible in the context of viral spread with the involvement of other organs [50].

This absence of correlation between ACE2 expression and infection susceptibility appears to be contradictory since ACE2 is the entryway to SARS-CoV-2 indicating that the larger expression of ACE2 in the membrane is in line with larger infectivity. However, COVID-19 elderly patients have superior severity of lung damage and a higher lethality rate in comparison with young people [1]. Then, young individuals are more susceptible to have the infection while old people with lower ACE2 expression could have a more severe condition in the case of infection due to the exacerbated effect mediated by the inhibition of AngII processing [51] even with individual variations on its expression level [52].

Aging is also associated with exuberant inflammatory cytokines secreted by senescent nonlymphoid cells that may cause organ dysfunction in humans and animal models [53]. Such excessive inflammation can inhibit antigen-specific immunity in vivo. Since (mammalian target of rapamycin) mTOR pathway is involved in the increase of the expression of IL-6 receptor and IL-6 secretion [54], the negative impact of inflammation on immunity during aging can be reversed in part by treatment with mTOR inhibitor rapamycin [55].

This review constitutes the initial background to understand how SARS-CoV-2 infection deregulates RAS in severe cases, and the impact on T cells and ARDS will enable novel therapeutic strategies to control the disease progression (Fig. 1).

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