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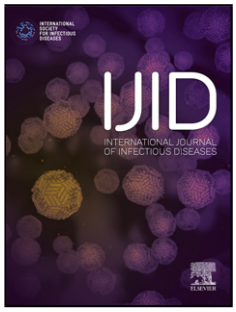

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PII: S1201-9712(20)32263-3

DOI: https://doi.org/10.1016/j.ijid.2020.10.059

Reference: IJID 4780

To appear in: *International Journal of Infectious Diseases*

Received Date: 25 May 2020

Revised Date: 16 October 2020

Accepted Date: 22 October 2020

Please cite this article as: { doi: https://doi.org/

Could SARS-CoV-2-induced lung injury be attenuated by vitamin D?

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Number of words: 2880

Number of figures: 5

Number of tables: 0

Competing financial interests

The authors have no conflicts of interest or funding to disclose.

Abbreviated title: Vitamin D and SARS-CoV-2

Keywords: SARS-CoV-2; coronavirus; vitamin D; acute lung injury; ARDS

Highlights

- As a counter-regulatory arm of the renin-angiotensin system (RAS), ACE2 plays critical roles in the pathogenesis of ARDS and acute lung injury.

- The affinity of the spike protein receptor binding domain (RBD) of the SARS-CoV-2 with human ACE2 (hACE2) largely determines the degree of clinical symptoms infected by SARS-CoV-2.
- Vitamin D was found to affect ACE2, the same target of SARS-CoV-2, we therefore propose that vitamin D might alleviate ARDS and acute lung injury induced by SARS-CoV-2 through modulating ACE2.

Abstract

A novel coronavirus (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) has been confirmed to have the capacity to transmit from humans to humans, causing acute respiratory distress syndrome (ARDS) and acute lung injury. Angiotensin converting enzyme-2 (ACE2) has been found to be expressed on type II pneumocytes. As a counterregulatory arm of the renin-angiotensin system (RAS), ACE2 plays critical roles in the pathogenesis of ARDS and acute lung injury. The affinity of the spike protein receptor binding domain (RBD) of SARS-CoV-2 with human ACE2 (hACE2) largely determines the degree of clinical symptoms after infection by SARS-CoV-2. Previous studies have revealed that regulating the ACE2/RAS system was effective in the treatment of severe acute respiratory syndrome coronavirus (SARS-CoV)-induced ARDS and acute lung injury. Since ACE2 is the host cell receptor of both SARS-CoV-2 and SARS-CoV, regulating the ACE2/RAS system may alleviate ARDS and acute lung injury caused by SARS-CoV-2 as well as SARS-CoV. Vitamin D was found to affect ACE2, the target of SARS-CoV-2; therefore, we propose that vitamin D might alleviate ARDS and acute lung injury induced by SARS-CoV-2 by modulating ACE2.

Introduction and general physiology

A novel coronavirus (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) has caused over 4761559 confirmed cases and over 317529 confirmed deaths worldwide as of May 20, 2020, 8:00 (https://www.who.int/emergencies/diseases/novel-coronavirus-2019). Many of the symptoms caused by SARS-CoV-2 are similar to those caused by severe acute respiratory syndrome coronavirus (SARS-CoV), especially acute respiratory distress syndrome (ARDS) (Li et al., 2020a). Previous studies have reported that ARDS is the primary cause of mortality and morbidity in intensive care units (ICUs) (Liu and Tan, 2020, Liu Wenshe et al., 2020, Liu Yingxia et al., 2020). ARDS is associated with increased alveolar epithelial permeability and pulmonary microvascular endothelial permeability, pulmonary oedema, and pulmonary fibrosis (Russell et al., 2020). The SARS-CoV envelope-anchored spike protein was shown to bind to the host receptor and then induce virus replication, and different structures of the SARS-CoV spike protein may bind to different target receptors (Li et al., 2020a, Li et al., 2020b, Wu et al., 2020). Thus, the surface structure of the spike protein is particularly important for the development of antiviral strategies (Zumla et al., 2020).

SARS-CoV-2 is a β-genus, single-stranded enveloped RNA virus (Li et al., 2020a). The genome sequences suggest that SARS-CoV-2 is closely associated with SARS and related viruses that circulate in bats (Li et al., 2020b). Almost 25% of the confirmed coronavirus disease 2019 (COVID-19) patients were reported to have severe and underlying comorbidities (Biscayart et al., 2020).

Evidence for the influence of angiotensin converting enzyme-2 (ACE2) on SARS-CoV-induced ARDS

The SARS epidemic occurred in southern China and caused more than 8000 cases of infection worldwide in 2002–2003, with an approximately 10% fatality rate (Li, 2013). The receptor-binding motif (RBM) of the spike protein of SARS-CoV directly contacts

ACE2 residues (Gui et al., 2017, Pak et al., 2009) (Figure 1). Mutations in the RBM affect the interactions of the spike protein and ACE2. For example, mutations at residues 479 and 487 of the RBM control the cross-species infections and human transmission of SARS-CoV, respectively (Ge et al., 2013, Li, 2013, Pak et al., 2009, Struck et al., 2012). Furthermore, the affinity of the spike protein receptor binding domain (RBD)/human ACE2 (hACE2) predominantly determines the degree of clinical symptoms caused by SARS-CoV (Gui et al., 2017, Mueller et al., 2012).

ACE2 has been found to be expressed on viral target cells, such as type II pneumocytes and enterocytes (Bertram et al., 2011). After SARS-CoV binds to ACE2, it triggers receptor-mediated endocytosis and the transport of virions into the endosomes of type II pneumocytes (Bertram et al., 2011, Gui et al., 2017, Haga et al., 2010). Then, the virus will replicate in the host cells, leading to downregulation of ACE2 (Li et al., 2020b). ACE2 is a novel ACE homologue that acts as a counterregulatory arm of the renin-angiotensin system (RAS) (Imai et al., 2008). This molecule can convert angiotensin I (Ang I) to Ang1-9 and convert Ang Ⅱ to Ang1-7 (Imai et al., 2008, Kuba et al., 2006). When Ang Ⅱ binds to the AT1a receptor, it will induce increased alveolar epithelial permeability and pulmonary microvascular endothelial permeability, pulmonary oedema, and pulmonary fibrosis. However, the opposite effects will occur when Ang Ⅱ binds to the AT2 receptor. In addition, as a counterregulatory arm of RAS, ACE2-Ang1-7 can bind to the Mas receptor to inhibit the above process to protect against lung injury (Li et al., 2016). The balance of Ang Ⅱ/Ang1-7 is commonly disrupted after infection with SARS-CoV; the ratio of Ang Ⅱ/Ang1-7 is increased due to decreased expression of ACE2, which can lead to acute lung injury and ARDS (Wu, 2020) (Figure 2).

The SARS-CoV spike protein was shown to bind to ACE2 and induce interleukin-8 (IL-8) release from lung cells by activating activation protein 1 (AP-1) (Chen et al., 2010). Dysregulation of inflammatory cytokines may be involved in ARDS. High levels of proinflammatory cytokines, such as transforming growth factor β (TGFβ), IL-8, IL-6, tumour necrosis factor alpha (TNF-α), interferon alpha (IFN-α), IFN-β, IFN-γ,

chemokine (C-C motif) ligand 3 (CCL3), CCL5 and CXCL10, were detected in SARS-CoV infection (Castilletti et al., 2005, Chen et al., 2010, Zhang et al., 2004, Ziegler et al., 2005). CCL2 is associated with ARDS and pulmonary fibrosis (Chen et al., 2010). CCL2 is overexpressed in SARS patients. Chen et al. (Chen et al., 2010) reported that SARS-CoV induced casein Ⅱ(CK Ⅱ)-mediated phosphorylation of the ACE2 receptor, activated ERK1/2, and upregulated AP-1/CCL2, thus leading to ARDS (Figure 3). Collectively, many studies have reported that ACE2 plays important roles in SARS-CoV-induced ARDS.

ACE2 protects the lung from acute injury

ACE2 overexpression can protect the lung from acute injury caused by viral and bacterial infections. Zou et al. demonstrated that H5N1 flu infection-induced lung injury could be alleviated by administrating recombinant hACE2 protein (Zou et al., 2014). Kuka et al. showed that higher levels of ACE2 are associated with better outcomes for coronavirus diseases (Kuba et al., 2006). In addition, overexpression of ACE2 alleviated lipopolysaccharide (LPS)-induced ARDS by activating the Ang1-7/Mas signalling pathway (Li et al., 2016).

ACE2 might affect SARS-CoV-2-induced ARDS: laboratory studies

SARS-CoV-2 viral infection can cause ARDS and acute lung injury, which are similar to those caused by SARS-CoV (Jin et al., 2020). ACE2 is the host cell receptor of both SARS-CoV-2 and SARS-CoV (Li, 2013, Wan et al., 2020, Zhou et al., 2020). Importantly, when the RBD binds to hACE2 with high affinity, the spike protein mediates viral entry into pneumocytes with strong efficiency (Wan et al., 2020). Wrapp et al. (Wrapp et al., 2020) found that the affinity of the SARS-CoV-2 spike protein binding to ACE2 was almost 20 times higher than that of the SARS-CoV spike protein, explaining why SARS-CoV-2 has a higher infection rate than SARS-CoV. A study by Bao (Bao et al., 2020) revealed that SARS-CoV-2 replication could be detected in the lungs of mice with hACE2 infected with SARS-CoV-2. These mice presented the typical histopathology of interstitial pneumonia, with infiltration of high levels of

macrophages and lymphocytes into the alveolar interstitium. In addition, SARS-CoV-2 antigens could be detected in bronchial epithelial cells, macrophages and alveolar epithelia. However, the above phenomenon was not found in wild-type mice with SARS-CoV-2 infection, suggesting that ACE2 is the key factor mediating SARS-CoV-2-induced lung damage. Since ACE2 is the target receptor of both SARS-CoV-2 and SARS-CoV, we hypothesize that the pathogenic mechanism of the two viruses might be very similar (Wu, 2020). Therefore, upregulating ACE2 and inhibiting RAS may alleviate ARDS and acute lung injury caused by SARS-CoV-2 as well as SARS-CoV (Wu, 2020). Xie et al. (Xie et al., 2006) investigated ACE2 expression in the lungs of a rodent model. These researchers found that the decrease in ACE2 was relatively slight between the young adult and the middle-aged groups, but the decrease was significant in older male rats compared to younger rats. This decrease in ACE2 with age may parallel the increase in COVID-19-related mortality in the older population.

ACE2 might affect SARS-CoV-2-induced ARDS: clinical studies

As the host cell receptor of SARS-CoV-2, ACE2 exists as a dimer that includes the N-terminal peptidase domain (PD) and the C-terminal collectrin-like domain (CLD) (Zhang et al., 2020). The PD of ACE2 recognizes the spike protein of SARS-CoV-2, and the CLD of ACE2 is cleaved by proteases such as transmembrane serine protease 2 (TMPRSS2), thus promoting SARS-CoV-2 spike protein-mediated entry into cells (Senapati et al., 2020). Specifically, decreased expression of proteins such as ACE2 and TMPRSS2 in the airway epithelium in children may reduce viral entry, which might be the reason why SARS-CoV-2 leads to decreased lung injury in children compared with adults (Lingappan et al., 2020). A study by Bobeck et al. reported that Ang II, an inhibitor of the RAS system, was safely used in a COVID-19 patient with cardiomyopathy and vasodilatory shock, with a rapid improvement in her haemodynamics and vasopressor requirement without adverse effects (Bobeck et al., 2020). In addition, Cheng et al. found that 44 patients with ARDS tolerated rhACE2 (Cheng et al., 2020).

The role of ACE polymorphisms in COVID-19

Since the affinity of the spike protein of SARS-CoV-2 for ACE2 predominantly determines the symptoms of patients with COVID-19, ACE allele frequency might affect the morbidity, infection course, severity and mortality of COVID-19 (Guo et al., 2020, Sieńko et al., 2020, Taha et al., 2020). A study by Guo revealed that the ACE structure could be changed by altered amino acids in missense variants. The His378Arg (rs142984500) mutant is a weak enhancer and the Ser19Pro (rs73635825) mutant is a strong enhancer of SARS-CoV-2 S-protein binding. The His378Arg (rs142984500) mutant may not only reduce the activity of ACE2 peptidase but also affect the process of SARS-CoV-2 S-protein and ACE2 binding. Additionally, the Ser19Pro (rs73635825) alteration may destabilize the helix of ACE2, affecting contact with the S-protein. Mutations such as Lys341Arg, Asp206Gly, Ile468Val, Arg219Cys/His, and Gly211Arg may significantly destabilize the local structure, and some of these mutations may have a minor effect on S-protein binding. The distribution of 12 characterized ACE2 missense variants in different populations was also identified by this study. Missense variants were present in East Asian (rs191860450), South Asian (rs751603885 and rs14877180), African (rs149039346, rs73635825, rs147311723 and rs138390800) and European (rs148771870) populations (Guo et al., 2020). These findings might help us recognize individuals with an increased risk of COVID-19.

Inflammatory cytokines induced by SARS-CoV-2

The major cytokines induced by SARS-CoV-2 include IL-2, IL-4, IL-6, IL-7, IL-10, granulocyte-colony stimulating factor (G-SCF), inducible protein-10 (IP-10), monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein 1 alpha (MIP1A), tumour necrosis factor α (TNF-α), and interferon-γ (IFN-γ), which were observed at high levels in severe COVID-19 patients (Hu et al., 2020, Song et al., 2020, Wang et al., 2020, Ye et al., 2020).

Collectively, SARS-CoV-2 primarily enters type Ⅱ pneumocytes with ACE2 and replicates with the help of TMPRSS2. Then, the replicated SARS-CoV-2 induces a cytokine storm, contributes to hyperinflammation and alveolar oedema and ultimately leads to ARDS.

Could SARS-CoV-2-induced lung injury be attenuated by vitamin D?

Vitamin D3 is mainly produced in the skin after exposure to ultraviolet rays from sunlight (Teymoori-Rad et al., 2019). The active form of vitamin D, 1,25(OH)D (1,25 dihydroxy vitamin D), binds to the vitamin D receptor (VDR) to play anti-inflammatory and immune regulatory roles (Gou et al., 2018, Xiao et al., 2019). VDR interacts with 1,25(OH)D and then binds to vitamin D responsive elements (VDREs) to inhibit or promote the expression of target genes, such as enhancement of ACE2 expression (Cui et al., 2019). Vitamin D deficiency is associated with increased pulmonary inflammation and ARDS in a mouse model; however, its effect is unclear in humans. Fitzgerald M et al. (Fitzgerald et al., 2015) found that healthy volunteers with vitamin D deficiency had increased pulmonary inflammation after LPS inhalation.

Ilie et al. (Ilie et al., 2020) found a negative correlation between vitamin D level and the number of COVID-19 cases in some countries, including Island, Norway, Sweden, Finland, Denmark, the UK, Ireland, the Netherlands, Belgium, Germany, France, Switzerland, Italy, Spain, Estonia, Czech Republic, Slovakia, Hungary, Turkey and Portugal. Furthermore, a negative correlation between vitamin D levels and the number of confirmed deaths caused by COVID-19 was also found in this study. There have been no actual data from the Chinese COVID-19 outbreak in relation to vitamin D levels until now. Vitamin D deficiency is common worldwide in all age groups due to decreased sun exposure and cutaneous synthesis, especially in northern regions. In particular, vitamin D deficiency is common among people during the winter and spring (particularly in the northern communities), especially in older and obese people (Orwoll et al., 2009). We speculate that the outbreak of COVID-19 in winter and spring may be partly due to higher vitamin D deficiency in these seasons.

Many studies have reported that vitamin D plays an important role in viral infections, such as those of the cold virus (Martineau et al., 2019, Science et al., 2013), rhinovirus (Schogler et al., 2016), influenza virus (Khare et al., 2013, Lee et al., 2018, Schogler et al., 2016), respiratory syncytial virus (RSV) (Teymoori-Rad et al., 2019), and adenovirus (Teymoori-Rad et al., 2019). Therefore, vitamin D might attenuate SARS-

CoV-2-induced lung injury.

Vitamin D and acute lung injury

Vitamin D and ACE2/RAS

ARDS and acute lung injury are associated with high fatality rates in patients affected by SARS-CoV-2 and SARS-CoV. ARDS and acute lung injury are associated with damaged pulmonary microvascular endothelial cells (PMVECs), which result in increased alveolar permeability and pulmonary oedema (Su et al., 2004). The balance between the expression of ACE1 and ACE2 is closely related to the ratio of Ang Ⅱ:Ang1-7, and an imbalance of Ang Ⅱ:Ang1-7 can lead to acute lung injury (Gao et al., 2019, Queiroz-Junior et al., 2019, Wang et al., 2018).

Increasing evidence indicates that 1,25(OH)D inhibits the RAS (Ali et al., 2018, Cui et al., 2019). The renoprotection of vitamin D is likely mediated by inhibiting the RAS, Ang Ⅱ and NF-kB, with a subsequent reduction in proinflammatory cytokines, such as IL-18 and TGF-β (Ali et al., 2018). After binding to Ang Ⅱ, AT1aR triggers NADPH oxidase (Nox) activation and generates reactive oxygen species (ROS) (Cui et al., 2019). VDR activation can inhibit the RAS to mediate antioxidant and anti-inflammatory effects (Cui et al., 2019).

VDR is widely distributed in lung cells. Vitamin D can alleviate acute lung injury by regulating RAS signalling (Xu et al., 2017). Pretreatment with calcitriol, a vitamin D agonist, significantly alleviated LPS-induced acute lung injury by upregulating ACE2 and downregulating ACE1, Ang Ⅱ, and AT1aR in an animal model (Xu et al., 2017) (Figure 4). Chronic vitamin D deficiency may activate the RAS and lead to lung fibrosis (Zhou et al., 2008).

Vitamin D and inflammatory cytokines

Vitamin D can significantly decrease inflammatory cytokines such as TNF-α, IL-8, IL-6, and IFN-β when exposed to influenza virus (Figure 5) (Khare et al., 2013). In addition, IFN-β was downregulated after RSV-infected human airway epithelial cells were treated with vitamin D (Hansdottir et al., 2010). IL-8, an endogenous chemotactic factor for neutrophils, is overexpressed in acute lung injury. Furthermore, $1,25(OH)_2D_3$ can

inhibit neutrophil infiltration and alleviate acute lung injury by downregulating IL-8 (Takano et al., 2011). Vitamin D/VDR signalling plays an important role in alleviating alveolar permeability and pulmonary oedema by decreasing proinflammatory cytokines (Shi et al., 2016).

Vitamin D and antimicrobial peptides

Vitamin D can induce the expression of antimicrobial peptides, which also have antiviral activity. Vitamin D was reported to bind to VDR and then increase the human cathelicidin peptide LL37 and human β- defensins (HBDs) (Teymoori-Rad et al., 2019) (Figure 5) in macrophages. LL37 can modulate Toll-like receptor (TLR) signalling and regulate inflammation (Schogler et al., 2016).

Collectively, vitamin D and SARS-CoV-2 can affect the same target, ACE2. Vitamin D might alleviate acute lung injury and ARDS induced by SARS-CoV-2 by regulating the RAS/ACE2 pathway, inflammatory cytokines, and antimicrobial peptides (Future 5).

Role of vitamin D supplementation in COVID-19 patients

Vitamin D supplementation might serve as a treatment to improve the clinical outcomes of COVID-19 patients. A previous report showed that 1,25(OH)D is inversely correlated with the risk of ARDS, heart failure, and diabetes mellitus (Grant et al., 2020). Ohaegbulam et al. (Ohaegbulam et al., 2020) reported 4 vitamin D-deficient COVID-19 patients who received treatment with vitamin D supplementation. The clinical outcomes included increased vitamin D levels, shorter lengths of hospital stay, lower oxygen requirements and reduced inflammatory markers. Another questionnaire-based study in Italy reported that vitamin D supplementation reduced the prevalence of COVID-19 infection (odds ratio, 0.56; 95% confidence interval, 0.32–0.99; p=0.048) (Fasano et al., 2020).

Conclusion and Future perspectives

Since ACE2 is the host cell receptor of both SARS-CoV-2 and SARS-CoV, regulating the ACE2/RAS system may alleviate lung injury caused by SARS-CoV-2 as well as SARS-CoV. Vitamin D was found to affect ACE2, the target of SARS-CoV-2. We speculate that vitamin D might alleviate lung injury induced by SARS-CoV-2 by

upregulating ACE2, decreasing inflammatory cytokines, and increasing antimicrobial peptides. The efficacy of vitamin D in treatment of SARS-CoV-2 needs to be verified through more evidence-based medicine. In the future, we hope randomized controlled clinical trials can be carried out to elucidate this issue.

Abbreviations

ACE2: angiotensin converting enzyme-2; Ang I: angiotensin I; Ang1-9: angiotensin 1-9; Ang Ⅱ: angiotensin Ⅱ; Ang1-7: angiotensin 1-7; AP-1: activation protein 1; ARDS: acute respiratory distress syndrome; ALI: acute lung injury; RAS: renin-angiotensin system; RBD: receptor binding domain; RBM: receptor-binding motif; 2019-nCoV: novel coronavirus; SARS-CoV: SARS coronavirus; VDR: vitamin D receptor; hACE2: human ACE2; TGF-β: transforming growth factor β; IL-8: inerleukin-8; TNF-α: tumour necrosis factor alpha; IFN-α: interferon alpha; CCL3: chemokine (C-C motif) ligand 3; VDREs: vitamin D responsive elements; RSV: respiratory syncytial virus; HBDs: β- defensins.

Ethics approval and consent to participate

Not applicable; review

Consent for publication

Not applicable; review

Clinical trial registration number and date if applicable

Not applicable; review

Availability of data and material

No additional data are available.

Conflict of Interest Statement

The authors declare that they have no competing financial interests.

Authors' contributions and Acknowledgements

Conceptualization, DX, XL and YQ; software, DX, XL, XS, DM and YQ; validation, DX, XL, XS, DM and YQ; investigation, DX, XL, XS, DM and YQ; resources, DX, XL, XS, DM and YQ; writing—original draft preparation, DX and XL; writing—review and editing, DX, XL, XS, DM and YQ; visualization, DM and YQ; supervision, DM and YQ; funding acquisition, DM and YQ. All authors read and approved the final manuscript.

Funding sources

This work was supported by the National Science Foundation of China (81971433, 81971428, 82001593, 82071353) and a grant from the Clinical Discipline Program (Neonatology) from the Ministry of Health of China (1311200003303).

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Competing financial interests

The authors have no conflicts of interest or funding to disclose.

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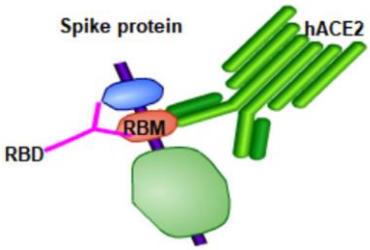
Figure captions

Figure 1. The RBM in the spike protein of SARS-CoV binding to human ACE2.



The RBM in red is the core of the RBD.

Figure 2. The role of ACE2 in acute lung injury.

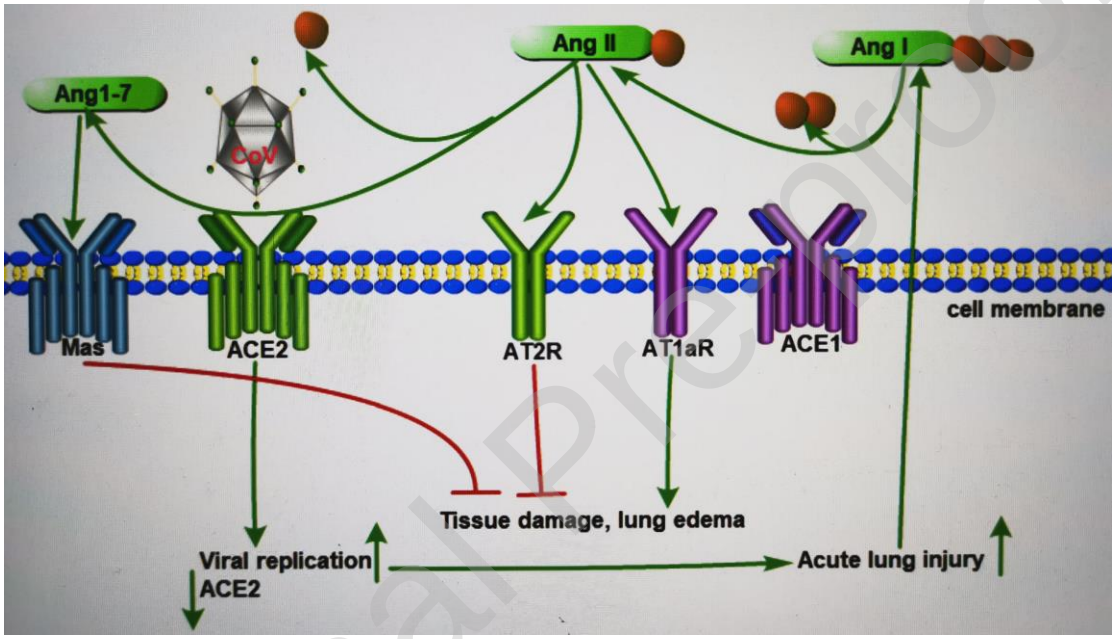


Figure 3. The role of ACE2/CCL2 signalling in lung fibrosis in SARS.

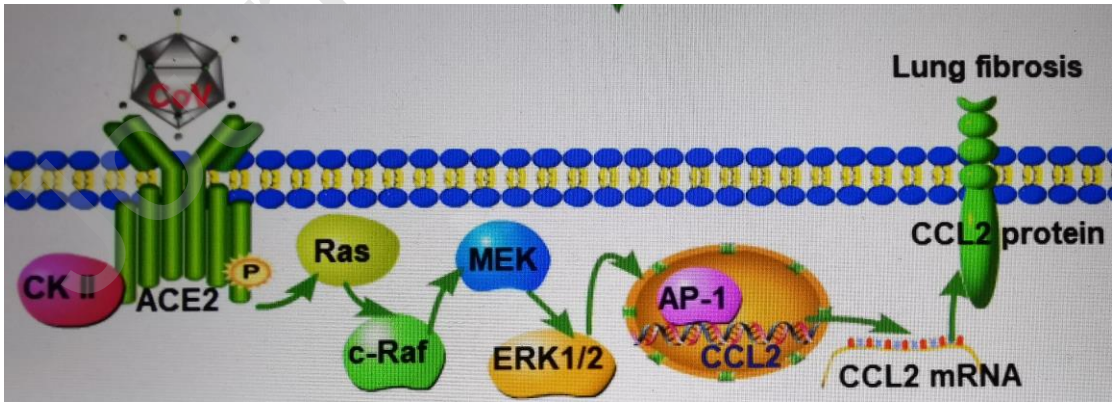


Figure 4. Vitamin D protects against acute lung injury.

Green: increased expression or promotion by vitamin D. Red: decreased expression or

inhibition by vitamin D. VDR, vitamin D receptor, VDREs, vitamin D responsive elements. Binding to the VDREs induces and represses the transcription of many genes.

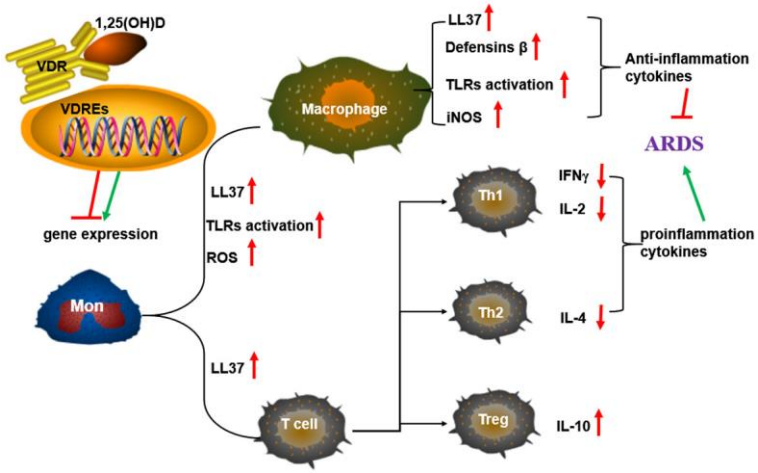


Figure 5. The possible mechanism by which vitamin D influences SARS-CoV-2.