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Cellular Immunology 360 (2021) 104259

Contents lists available at ScienceDirect

Cellular Immunology

journal homepage: www.elsevier.com/locate/ycimm

Review article

Effects of vitamin D on macrophages and myeloid-derived suppressor cells (MDSCs) hyperinflammatory response in the lungs of COVID-19 patients

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ARTICLE INFO

Keywords:
Macrophages
Myeloid-derived suppressor cells (MDSCs)
Hyperinflammatory response
Vitamin D
Vitamin D receptor
COVID-19
SARS-CoV-2

ABSTRACT

Vitamin D regulates homeostasis, anti-microbial response, and inflammation. The vitamin D receptors are expressed in the macrophages and other immune cells, regulating the transcription of many different genes, including those coding the anti-microbial peptides. One of the most severe complications of the SARS-CoV-2 infection is the acute respiratory distress syndrome (ARDS) caused by the hyperinflammatory response (commonly called cytokine storm) of the lung macrophages. Studies showed that Vitamin D deficiency increases the severity of the ARDS in COVID-19 infection. We discuss here how the vitamin D supplementation may influence macrophage and myeloid-derived suppressor cells (MDSCs) inflammatory response, subdue the hyperinflammatory response, and lessen the ARDS in COVID-19 patients.

1. Introduction

COVID-19 pandemic has revived and increased interest in vitamin D as a potential modulator of the immune response in SARS-CoV-2 infection. As the macrophage immune response plays an important role in the severity of COVID-19, any factor modulating their functions is, currently, of the high interests. Besides macrophages, the myeloid-derived suppressor cells (MDSCs), which suppress T cells activity and attenuate the overall immune response, are also the target of Vitamin D. This indicates that Vitamin D may have therapeutic applications as an additive to conventional anti-viral therapies.

Vitamin D (25 $(OH)_2$ D) is a fat-soluble secosteroid (steroid with a "broken" ring) hormone that regulates absorption and homeostasis of magnesium, calcium and phosphate, and various aspects of human health, including mitochondrial integrity, systemic inflammation, and the anti-microbial immune response [1–2]. The active metabolite of vitamin D, the 1, 25 dihydroxy vitamin D (1,25 $(OH)_2$D3) that circulates in the blood, functions through the binding to vitamin D receptor (VDR), also called the NR1I1 (nuclear receptor subfamily 1, group I, member 1), which is the member of the nuclear receptor family of transcription factors. The 1,25 $(OH)_2$ D/VDR complex heterodimerizes with the retinoic-X receptor (RXR), causing nuclear translocation, and binding to the vitamin D response elements (VDREs) on DNA. This, in turn, dissociates repressors, recruits the co-factors, and regulates the transcription of over 900 different genes (Fig. 1); [3–6]. Because the VDR is also abundantly expressed in the immune cells such as T cells, dendritic cells, and macrophages, many of these target genes have immune response-related functions [4]. For example, such targets are the cathelicidin, and defensin, genes that encode the anti-microbial peptides that reduce viral replication rate and promote chemotaxis of macrophages and other immune cells to the inflamed organs [3,7,8].

2. Macrophages and hyperinflammatory response in the lungs of COVID-19 patients

One of the deadliest effects of SARS-CoV-2 infection is the acute

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https://doi.org/10.1016/j.cellimm.2020.104259
Received 11 October 2020; Received in revised form 3 December 2020; Accepted 5 December 2020
Available online 16 December 2020

respiratory distress syndrome (ARDS) caused by the overdrive of the inflammatory response of lung macrophages (Fig. 2); [9–16]. There are two different (intrinsic and extrinsic) mechanisms inducing macrophage inflammatory response. In the intrinsic response, the alveolar macrophages, express the ACE2 (angiotensin-converting enzyme-2), which acts as the receptor recognizing spike proteins on the surface of SARS-CoV-2 and similar viruses (SARS-CoV, and NL63), and facilitates virus entry, are infected with the virus [17,18]. This, in turn, switches on a rapid and severe immune response flooding the lungs with the inflammatory cytokines and factors such as tumor necrosis factors (TNFs), IL-1, IL-6, IL-8, and IL-12, and many others [16,19], which affect B cells, neutrophils, basophils, and T cells, sending additional pro-inflammatory signals to macrophages and amplifying the inflammatory response [19]. In the extrinsic response, the macrophage immune response is induced by the incoming inflammatory signals from the lung epithelial cells (that also express ACE2 and are infected by the virus), macrophages in the pulmonary lymph nodes and spleen, or/and immune cells of other infected organs. The produced cytokines, and chemokines (cytokines which have a chemotactic function) can also recruit monocytes and additional macrophages to the lungs propagating further inflammatory response [19]. Some studies show that the effectiveness of the currently used anti-inflammatory therapies for the treatment of various diseases relies not only on the inhibition of cytokine production but also on the decrease of macrophage infiltration [15].

3. Molecular mechanisms of vitamin D effects on the hyperinflammatory response in COVID-19

Recent analyses of COVID-19 patients' data from Germany, UK, US, France, Spain, Italy, China, and South Korea showed that a severe vitamin D deficiency correlates with a high

(C-Reactive Protein) CRP level in patients with COVID 19 infection [10]. As we described in previous sections, the ARDS is caused by the overdrive of the lung macrophage and other immune cells (B cells, neutrophils, basophils, and T cells) inflammatory response [19]. Here we discuss how vitamin D may be involved in the modulation/suppression of macrophage response in the COVID-19 patients. Such a suppressing effect of vitamin D on the hyperinflammatory response was already suggested during the influenza pandemic in 1918–1919 [20].

4. Expression and role of vitamin D receptors

The response to and modulation of immune cells activity by vitamin D depends on the vitamin D receptors expressed by these cells. One of the recently proven functions of VDRs is the prevention of the immune response of T cells and dendritic cells [4]. Mouse studies showed that VDR-KOs have more pro-inflammatory Th17 effector cells, which produce more IL-17 [4,21]. In contrast, the upregulation of VDR expression inhibits transcription of the IL-2 gene and prevents the immune system overdrive. Similarly, it has been shown that vitamin D, by promoting the development of tolerogenic dendritic cells and the suppressive iTregs involved in immune tolerance, prevents potential over-reaction of the immune system [4,22]. The VDR is also crucial for the integrity of mitochondria and prevents increased respiratory activity and production of damaging reactive oxygen species (ROS) that are the important activators of pro-inflammatory signaling in the macrophages [23–25].

Already one hundred years ago, in the pre-antibiotic era, the increase of vitamin D by sun exposure or fish oil consumptions was used for the

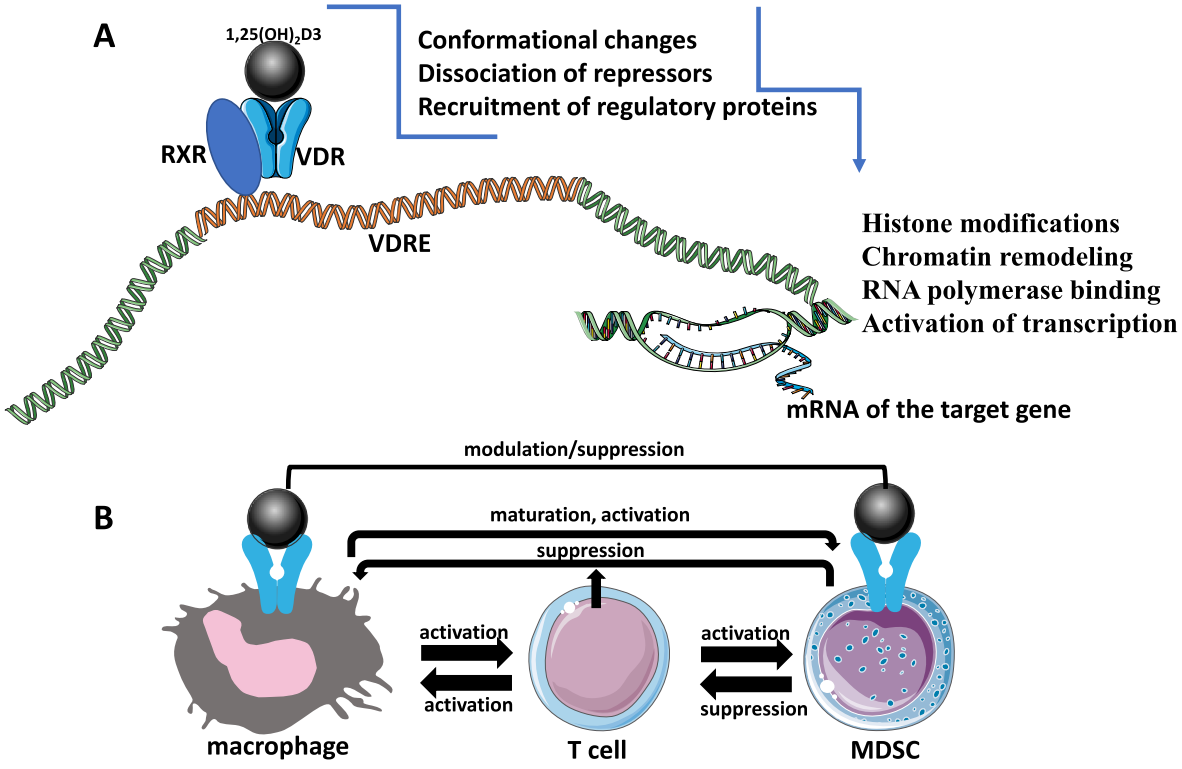

Fig. 1. Regulation of transcription and activities of immune cells by vitamin D. A) The hormonal metabolite of vitamin D, the 1,25-dihydroxyvitamin D (1,25 $(OH)_2D3$) is the ligand for the vitamin D receptor (VDR). In the absence of the 1,25$(OH)_2D3$, the VDR is localized in the cytoplasm. Interaction of VDR with the 1,25 $(OH)_2D3$ causes heterodimerization with the retinoid X receptor (RXR). This complex translocates to the nucleus where it binds to the vitamin D responsive element (VDRE) of the vitamin D-responsive genes. Further recruitment of regulatory factors, dissociation of repressors, histone modification, and chromatin remodeling, induce RNA polymerase binding and activate transcription of the target gene(s). B) Reciprocal effect between the macrophages, T cells, and MDSCs. Inflammatory signaling from the macrophages mature and activate MDSCs, and T cells regulate the activity of MDSCs [56]. The MDSCs may also suppress the function of T cells and this, in turn, indirectly, may suppresses the activity of other immune cells. Vitamin D affects transcription and protein expression in macrophages and MDSCs and modulates the inflammatory response. Although not shown here, the T cells also express VDR, and they are also directly affected by the vitamin D supplementation.

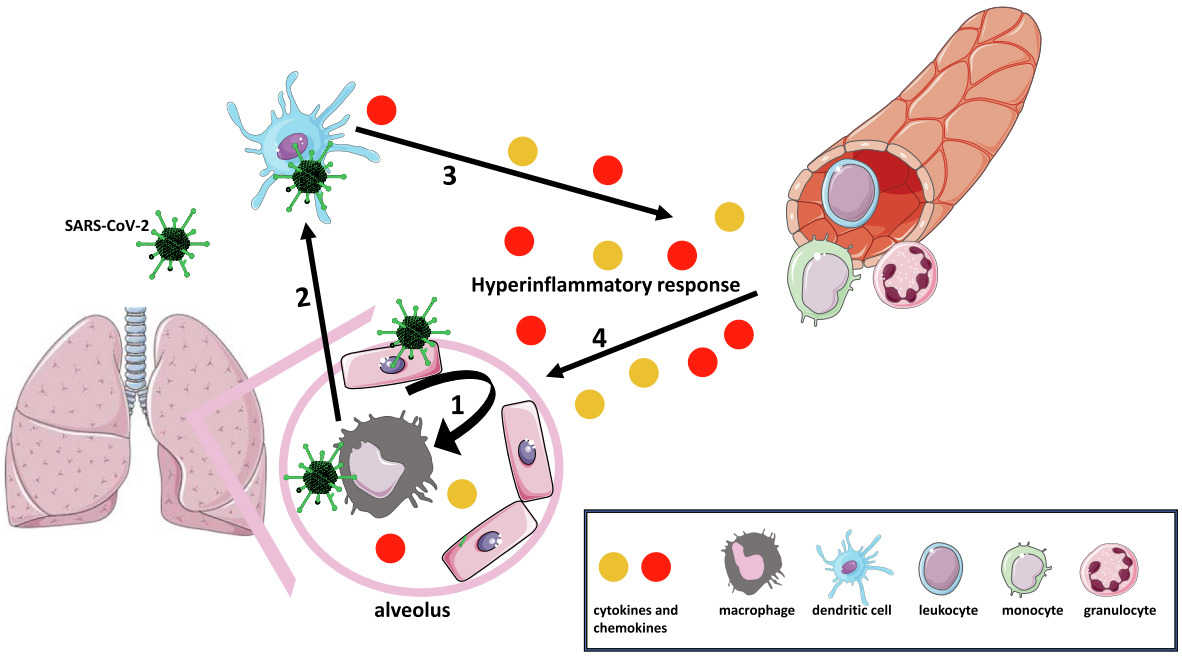

Fig. 2. Hyperinflammatory response induced by alveolar macrophages. Arrow 1. The SARS-CoV-2 virus infects, through the ACE2 receptors the alveolar macrophages and alveolar epithelial cells that induces the production of proinflammatory cytokines by the macrophages.The infected epithelial cells send the proinflammatory signals to the alveolar macrophages enhancing macrophage response and sending inflammatory signals to other immune cells. Arrow 2. The virus also infects the dendritic cells, which also produce proinflammatory cytokines and chemokines. Arrow 3. All these pro-inflammatory factors recruit monocytes, granulocytes, and various leukocytes from the circulation. The recruited immune cells produce more cytokines and chemokines amplifying the proinflammatory response. Arrow 4. Such an overdrive of the inflammatory response causes the hyperinflammatory response in the lungs and the acute respiratory distress syndrome (ARDS) in the COVID-19 patients.

treatment of tuberculosis, and the vitamin D supplementation may still be considered today as a beneficial adjunct to the antibiotic therapy for pulmonary tuberculosis [26,27]. Recent studies showed that macrophages, including alveolar macrophages that are crucial for the development of the hyperinflammatory response in the lungs of COVID-19 patients, have an inducible expression of vitamin D 1α-hydroxylase Cyp27B1 that converts the inactive form of vitamin D to its active metabolite 1,25 $(OH)_2$) D that binds macrophage VDRs [28]. Studies also showed that the genetic deletion of macrophage VDRs, which are activated either by the circulatory or macrophage-produced 1,25 $(OH)_2$ D, impairs the immune response to cutaneous injury in mouse wound-healing model [29]. Zhang et al. [30] showed that vitamin D treatment increased the binding of the VDR to the vitamin D response element in the promoter of the mitogen-activated protein kinase phosphatase-1 (MKP-1) promoter. This caused the upregulation of MKP-1 expression, and, in turn, inhibited the production of pro-inflammatory IL-6 and TNF-α in the monocytes and macrophages. It is still unknown if in the response to vitamin D, the VDR receptors, which regulate gene transcription, become localized in the cell nucleus permanently or if they shuttle between the nucleus and cytoplasm [31]. Studies on the chronic inflammatory lung disease such as cystic fibrosis showed that vitamin D, acting through its receptors, upregulates transcription of the anti-inflammatory Dual specificity protein phosphatase 1 (DUSP1) gene, which down-regulates the expression of inflammatory chemokine IL-8 produced by over-reactive (hyperinflammatory) macrophages [32]. This suggests a therapeutic potential of vitamin D for the treatment of inflammatory lung diseases. Also, a recent large-scale analysis of COVID-19 patients suggests that vitamin D activates the innate, and suppresses the adaptive immune response, which, by lowering the cytokine expression level may downregulate the hyperinflammatory response responsible for COVID-19 severity and mortality [10,33–35]. In line with these findings, the National Institute of Health posted on their ClinicalTrials gov. website, several clinical trials, which will assess the efficacy of vitamin D in the prevention and treatment of COVID-19. A recent studies by Rastogi and colleagues [36] show that a high dose of vitamin D supplementation by oral administration helped to achieve SARS-CoV-2 RNA negativity along with a significant decrease of the inflammatory markers (Fig. 1). Moreover, Maghbooli and co-authors [37] have shown very recently that the correct levels of 25-hydroxyvitamin D reduce the risk of cytokin storm and the heavy course of COVID-19 in patients.

5. Potential functions of myeloid-derived suppressor cells (MDSCs) in COVID-19

The myeloid-derived suppressor cells (MDSCs) exit from the bone marrow as functionally immature cells. Depending on the signals from the microenvironment they mature into monocytic MDSCs (mMDSCs) and granulocytic MDSCs (gMDSCs). They suppress the *T*-cell cycle and immune checkpoints, downregulate T cell receptors, and recruit Tregs ([38]). They also suppress the activity of other immune cells through the production of ROS, RNS, degradation of L-arginine, and the production of the anti-inflammatory factors, such as (TGF)-β and IL-10 [39] , (Fig. 1).

Recent studies indicated that the granulocyte-colony-stimulating factor (G-CSF) granulocyte–macrophage colony-stimulating factor (GM-CSF), which are the main factors driving recruitment and differentiation of MDSCs are abundant in the lungs of COVID-19 patients. Recent analyses of MDSCs in 128 SARS-CoV-2 infected patients, showed a very high frequency of MDSCs, especially in the intensive care patients. It is very plausible that the immunosuppressive function of MDSCs prevented virus elimination and increased the severity of the disease [40]. This suggests that the MDSCs may be a valuable target for therapeutic intervention in COVID-19 patients [41]. Like other immune cells, the MDSCs express Vitamin D receptors, and as such can be a target for vitamin D intervention [42]. Studies also show that the level of expression of VDRs correlates with the immunosuppressive activity of MDSCs and that the active form of vitamin D, 1,25(OH)2D, reduces the

suppressive activities of MDSCs by 70%, especially in the early stages of their maturation [42].

6. Vitamin D in COVID-19 pediatric patients

It is now well established that children are less frequently infected with SARS-CoV-2 and are more often either asymptomatic or suffer less severe symptoms than adults [43–50]. The immune system of newborns and very young children is not yet fully developed [51] , and their innate immune response based on monocytes, macrophages, dendritic cells, and neutrophils seem to work differently than in the adults and is associated with clearly lower cytokine response. For instance, De Wit and coworkers showed impaired production of IL-12 and IFN- α and an increased synthesis of IL-10 in the neonatal cord blood after the exposure to TLR-4 and TLR-3 ligands, in comparison to the adult blood, which may indicate an impaired anti-viral and anti-Gram-negative bacteria response in the neonates [52]. This under-responsiveness may protect, in part, SARS-CoV-2 infected children against the hyper-inflammatory response. The immune response of children is also clearly different than in adults with respect to the production of the antibodies [53]. In short, adults produce anti-spike (S) IgG, IgM, and IgA antibodies, and anti-nucleocapsid IgG antibody, while children have much lower levels of anti-SARS-CoV-2-specific antibodies, and predominantly generate IgG antibodies specific for the S protein, but not against the nucleocapsid proteins. Moreover, children's antibodies have much less pronounced neutralizing activity than the antibodies of adult patients. The authors concluded that children clear SARS-CoV-2 faster than adults, probably via more efficient and adequate innate immunological response due to macrophages involvement.

Another important point is that in the developed countries the newborns receive vitamin D supplementation soon after birth, while in the subtropical and tropical countries babies and young children are exposed to the sunlight, which supplements them with vitamin D naturally. Another factor may be the presence of other respiratory viruses common in young children, which could competetively limit the growth of SARS-CoV2 [54]. A recent large non-pediatric study reveals the cross-reactivity between the SARS-CoV-2 antigens and the antibodies presumably originating from the previous human coronaviruses infections [55]. As children get these diseases more often than adults and possibly had these infections not long before the COVID-19 pandemic, they have statistically more chances to be protected by this cross-reactivity than adults.

In summary, it seems that vitamin D supplementation should have beneficial effects by lessening the macrophage-dependent hyper-inflammatory response in the lungs of COVID-19 patients. This supplementation is of special interest in the northern hemisphere during the second wave of COVID-19 pandemic in winter 2020/2021.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

While writing this article JZK was supported by the grant "Kościuszko" # 5508/2017/DA from the Polish Ministry of National Defense.

We acknowledge that some of the images used to make figures were from the Servier Medical ART: SMART, http://smart.servier.com.

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