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

Malgorzata Kloc*[1,2,3], Rafik M. Ghobrial[1,2], Agnieszka Lipińska-Opałka[4], Agata Wawrzyniak[4] , Robert Zdanowski[5], Boleslaw Kalicki[4] , Jacek Z Kubiak*[, 6, 7]

[1]The Houston Methodist Research Institute, Houston, Texas 77030, USA

[2]The Houston Methodist Hospital, Department of Surgery, Houston, Texas, USA

[3]The University of Texas, M.D. Anderson Cancer Center, Department of Genetics, Houston Texas, USA

[4]Military Institute of Medicine, Clinic of Paediatrics, Nephrology and Child Allergology, Central Clinical Hospital of the Ministry of National Defense, Warsaw, Poland

[5]Laboratory of Molecular Oncology and Innovative Therapies, Military Institute of Medicine (WIM), Warsaw, Poland

[6]Laboratory of Regenerative Medicine and Cell Biology, Military Institute of Hygiene and Epidemiology (WIHE), Warsaw, Poland

[7]UnivRennes, UMR 6290, CNRS, Institute of Genetics and Development of Rennes, Cell Cycle Group, Faculty of Medicine, Rennes, France

Corresponding authors:

Malgorzata Kloc, The Houston Methodist Research Institute, 6670 Bertner Ave, Houston, TX 77030, USA; email: mkloc@houstonmethodist.org

and

Jacek Z Kubiak, UMR 6290, CNRS/UR1, IGDR, Faculty of Medicine, 2 Ave. du Prof. Leon Bernard, 35043 Rennes cedex, France; e-mail: jacek.kubiak@univ-rennes1.fr

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

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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.

Key words: macrophages, myeloid-derived suppressor cells (MDSCs), hyperinflammatory response, vitamin D, vitamin D receptor, COVID-19, SARS-CoV-2

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, 4). 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).

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

One of the deadliest effects of SARS-CoV-2 infection is the acute respiratory distress syndrome (ARDS) caused by the overdrive of the inflammatory response of lung macrophages (Fig. 2); (9-16).

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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).

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).

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

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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 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

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136 achieve SARS-CoV-2 RNA negativity along with a significant decrease of the inflammatory markers
137 (Fig 1).
138
139 **Potential functions of myeloid-derived suppressor cells (MDSCs) in COVID-19**
140 The myeloid-derived suppressor cells (MDSCs) exit from the bone marrow as functionally immature
141 cells. Depending on the signals from the microenvironment they mature into monocytic MDSCs
142 (mMDSCs) and granulocytic MDSCs (gMDSCs). They suppress the T-cell cycle and immune
143 checkpoints, downregulate T cell receptors, and recruit Tregs (37). They also suppress the activity of
144 other immune cells through the production of ROS, RNS, degradation of L-arginine, and the
145 production of the anti-inflammatory factors, such as (TGF)-β and IL-10 (38), (Fig.1).
146 Recent studies indicated that the granulocyte-colony-stimulating factor (G-CSF) granulocyte-
147 macrophage colony-stimulating factor (GM-CSF), which are the main factors driving recruitment and
148 differentiation of MDSCs are abundant in the lungs of COVID-19 patients. Recent analyses of
149 MDSCs in 128 SARS-CoV-2 infected patients, showed a very high frequency of MDSCs, especially
150 in the intensive care patients. It is very plausible that the immunosuppressive function of MDSCs
151 prevented virus elimination and increased the severity of the disease (39). This suggests that the
152 MDSCs may be a valuable target for therapeutic intervention in COVID-19 patients (40). Like other
153 immune cells, the MDSCs express Vitamin D receptors, and as such can be a target for vitamin D
154 intervention (41). Studies also show that the level of expression of VDRs correlates with the
155 immunosuppressive activity of MDSCs and that the active form of vitamin D, 1,25(OH)2D, reduces
156 the suppressive activities of MDSCs by 70%, especially in the early stages of their maturation (41)
157
158 **Vitamin D in COVID-19 pediatric patients**
159 It is now well established that children are less frequently infected with SARS-CoV-2 and are more
160 often either asymptomatic or suffer less severe symptoms than adults (42-49). The immune system of
161 newborns and very young children is not yet fully developed (50), and their innate immune response
162 based on monocytes, macrophages, dendritic cells, and neutrophils seem to work differently than in
163 the adults and is associated with clearly lower cytokine response. For instance, De Wit and coworkers
164 showed impaired production of IL-12 and IFN- α and an increased synthesis of IL-10 in the neonatal
165 cord blood after the exposure to TLR-4 and TLR-3 ligands, in comparison to the adult blood, which
166 may indicate an impaired anti-viral and anti-Gram-negative bacteria response in the neonates (51).
167 This under-responsiveness may protect, in part, SARS-CoV-2 infected children against the
168 hyperinflammatory response. The immune response of children is also clearly different than in adults
169 with respect to the production of the antibodies (52). In short, adults produce anti-spike (S) IgG, IgM,

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170 and IgA antibodies, and anti-nucleocapsid IgG antibody, while children have much lower levels of
171 anti-SARS-CoV-2-specific antibodies, and predominantly generate IgG antibodies specific for the S
172 protein, but not against the nucleocapsid proteins. Moreover, children`s antibodies have much less
173 pronounced neutralizing activity than the antibodies of adult patients. The authors concluded that
174 children clear SARS-CoV-2 faster than adults, probably via more efficient and adequate innate
175 immunological response due to macrophages involvement.
176 Another important point is that in the developed countries the newborns receive vitamin D
177 supplementation soon after birth, while in the subtropical and tropical countries babies and young
178 children are exposed to the sunlight, which supplements them with vitamin D naturally. Another
179 factor may be the presence of other respiratory viruses common in young children, which could
180 competetively limit the growth of SARS-CoV2 (53). A recent large non-pediatric study reveals the
181 cross-reactivity between the SARS-CoV-2 antigens and the antibodies presumably originating from
182 the previous human coronaviruses infections (54). As children get these diseases more often than
183 adults and possibly had these infections not long before the COVID-19 pandemic, they have
184 statistically more chances to be protected by this cross-reactivity than adults.
185 In summary, it seems that vitamin D supplementation should have beneficial effects by lessening the
186 macrophage-dependent hyperinflammatory response in the lungs of COVID-19 patients. This
187 supplementation is of special interest in the northern hemisphere during the second wave of COVID-
188 19 pandemic in winter 2020/2021.
189

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196 **Conflict of interests statement**
197 None of the authors has any conflict of interests
198
199 **References**
200

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Figure Legends

Figure 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$(OH)_2$D3) is the ligand for the vitamin D receptor (VDR). In the absence of the 1,25$(OH)_2$D3, the VDR is localized in the cytoplasm. Interaction of VDR with the 1,25$(OH)_2$D3 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 [55]. 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.

Figure 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.

Highlights

Vitamin D deficiency increases the severity of the ARDS in COVID-19 infection
Vitamin D receptors are expressed in the macrophages and other immune cells

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Vitamin D supplementation may influence macrophage inflammatory response, subdue the cytokine storm and lessen the ARDS in COVID-19 patients

FIG. 1

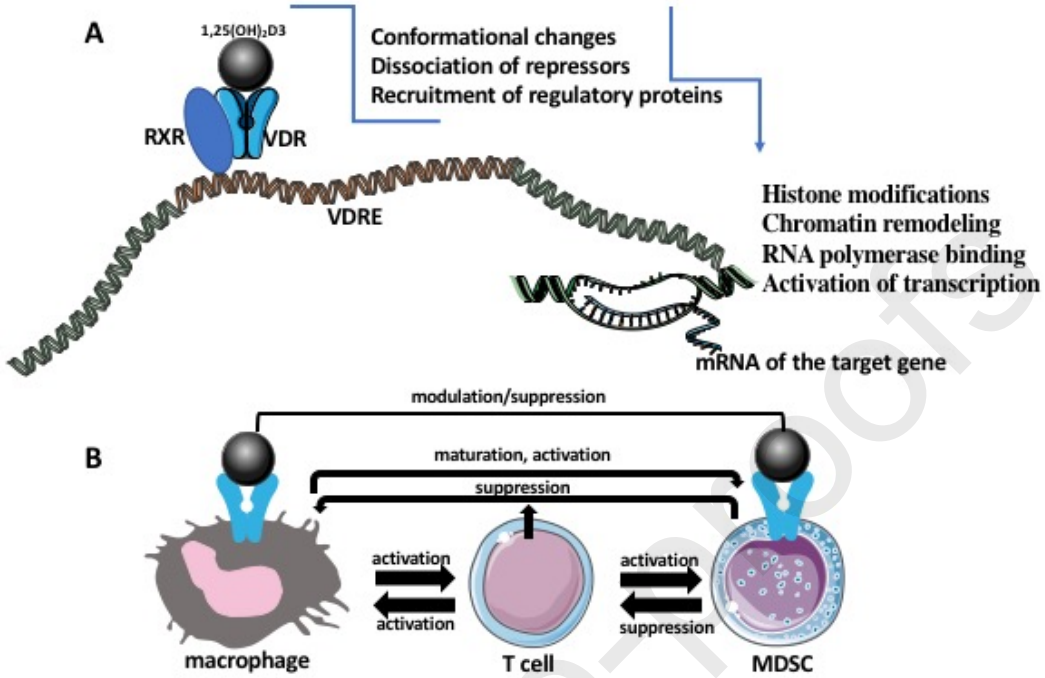
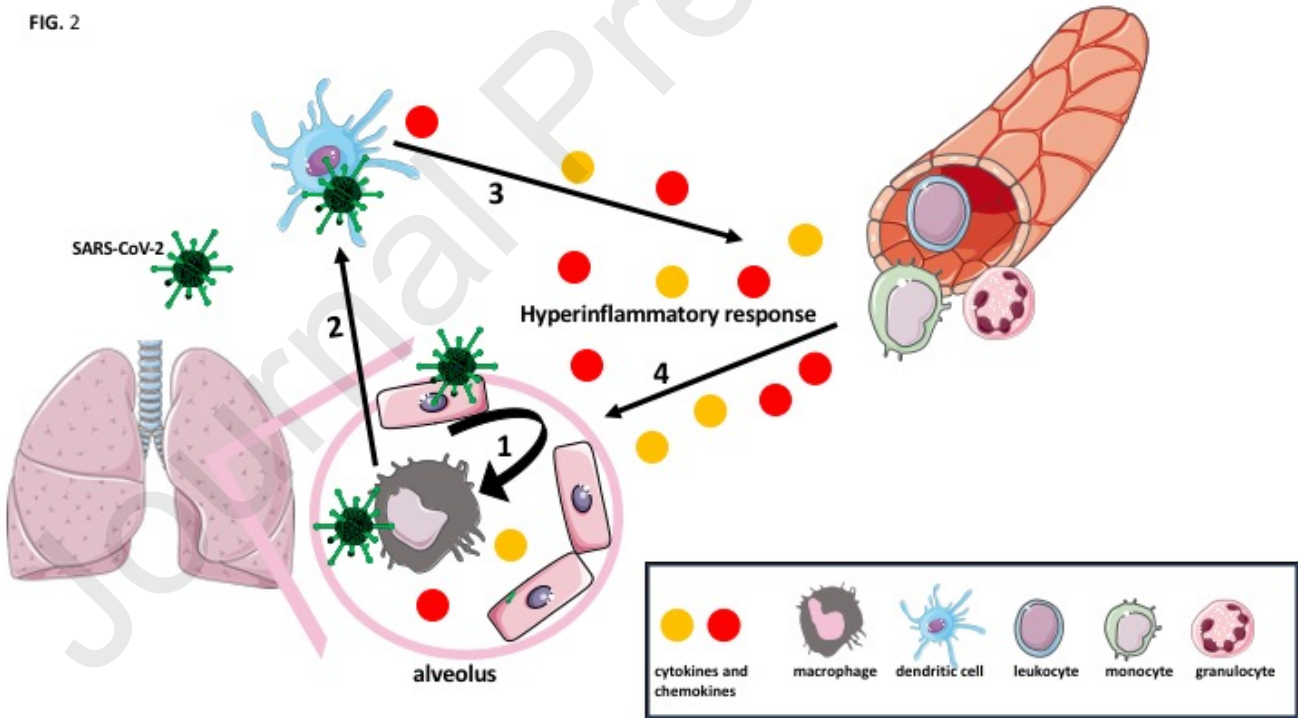


FIG. 2



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