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Review Article

Vitamin D and pulmonary fibrosis: a review of molecular mechanisms

Dandan Ma[1], Lipan Peng[2]

[1]*Department of Critical-Care Medicine, Affiliated Jining First People's Hospital, Shandong, China;* [2]*Department of Gastrointestinal Surgery, Shandong Provincial Hospital Affiliated to Shandong University, Jinan 250000, Shandong, China*

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Abstract: Pulmonary fibrosis is a serious interstitial disease characterized by initial diffuse alveolar inflammation, fibroblast proliferation, ECM accumulation, and the destruction of normal pulmonary tissues, whose etiology remains unknown and therapeutic options remain limited. The prevalence of Vitamin D deficiency is increasing and has been linked to pulmonary fibrosis. In recent years, many studies focused on the mechanistic pathway of Vitamin D in the prevention of fibrosis. This review highlights the current evidence on the molecular mechanisms of Vitamin D in pulmonary fibrosis. We want to provide new clues to the clinical management of pulmonary fibrosis.

Keywords: Vitamin D, vitamin D receptor, VDR, pulmonary fibrosis

Introduction

Pulmonary fibrosis describes a progressive and irreversible lung disease, with a mean life expectancy of only 3-5 years [1-5], posing a big threat to public health. Common symptoms caused by pulmonary fibrosis such as fatigue, cough, and dyspnea have a major impact on the quality of life (QOL) of patients [6]. Its etiology remains elusive and therapeutic options remain limited. Until now, there is no pharmacological therapy but lung transplantation to change the natural course of the disease.

Pulmonary fibrosis is a wound healing response caused by lung injury and infection. However, chronic exposure to the injury factor such as allergens, toxic chemicals, and radiation leads to dysregulated wound healing response, overlapping inflammation and subsequent pulmonary fibrosis [2]. Finally the scar tissues take the place of normal lung architecture [7]. To date, the potential molecular mechanism of pulmonary fibrosis is still unknown. But it is closely related to the regulation of collagen-secreting myofibroblasts proliferation, activation, and differentiation, and inflammation.

Vitamin D has long been regarded as a key player in calcium homeostasis, bone health, electrolyte and blood pressure regulation and immune response [8, 9]. It is provided by the kidney and parathyroid gland endocrine system. To achieve full biologic activity, Vitamin D must be metabolized to the hormonal form 1,25-dihydroxy Vitamin D by the activating hydroxylase the Vitamin D 25-hydroxylase, and 1-αhydroxylase [10]. As is known to all, Vitamin D is distributed not only to the liver but also to all tissues in the human body. For the moment, many of these tissues are now found to contain many hydroxylases that alters Vitamin D into 1,25-dihydroxy Vitamin D, thus the autocrine production of 1,25-dihydroxy Vitamin D in those tissues occurs [11-14]. The biologically active metabolite of 1,25-dihydroxy Vitamin D is thought to exert its principal actions by binding to the Vitamin D receptor (VDR, a ligand-dependent transcription factor) [15].

However, vitamin D is not just a vitamin; the pleiotropic roles of Vitamin D have been highlighted in various diseases. Vitamin D is related to cell proliferation, differentiation, apoptosis, intercellular adhesion, oxidative stress, matrix homeostasis, and regulation of inflammatory

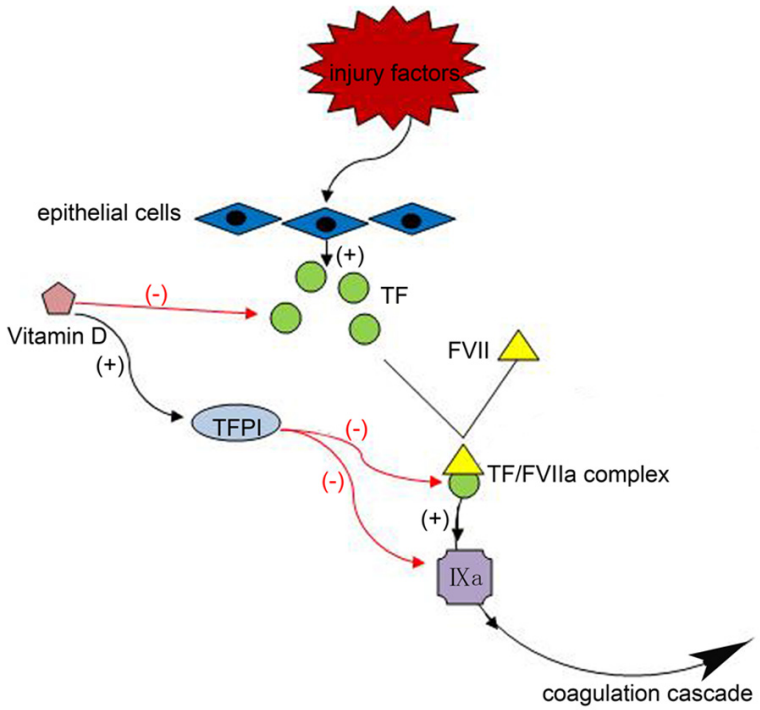

Figure 1. When epithelial cells get stimulated by injury factors, they will release TF, and then together with activated factor VIIa (FVIIa) formed TF/FVIIa complex, which activate factor IX, this is the primary initiator of coagulation cascade. Vitamin D can exert anticoagulant effects in two ways: (1) Vitamin D suppresses TF expression, (2) Vitamin D increases the levels of TFPI.

response [16-18]. The association between serum Vitamin D and pulmonary fibrosis has become a hot topic in recent years. Vitamin D affects the progress of pulmonary fibrosisa variety of ways. This review gives a more detailed and integrated elaboration on the mechanistic pathway of Vitamin D in prevention of pulmonary fibrosis.

The distinct stages of pulmonary fibrosis and vitamin D

Pulmonary fibrosis is an abnormal wound healing response caused by lung injury and infection, which has four distinct stages: a clotting/coagulation phase, an inflammatory phase, a fibroblast migration/proliferation/activation phase, and a tissue remodeling and resolution phase [7]; pulmonary fibrosis usually occurs if any stage in the tissue repair process is dysregulated.

A clotting/coagulation phase

When epithelial cells are stimulated by injury factors, they release inflammatory mediators and then activate an antifibrinolytic coagulation cascade. Unfortunately, the excessive activation of the coagulation cascade has been seen throughout the process of pulmonary fibrosis [19, 20]. Recent studies implicated that the coagulation factors are predominantly mediated by protease-activated receptors (PARs), and PARs play a significant role in the pathogenesis of lung fibrosis [19, 21-23]. This family comprises four members (PAR1, PAR2, PAR3, and PAR4) but current evidence suggests PAR1 play a major role in the context of lung injury. PARs mediates tissue factor (TF) [24, 25], then TF together with activated factor VIIa (FVIIa) forms TF/FVIIa complex. The TF/FVIIa is the primary initiator of the coagulation cascade, which activates factor IX, but is blocked by the TF pathway inhibitor (TFPI), a protease inhibitor.

Vitamin D can exert anticoagulant effects by two predominant ways (**Figure 1**): 1) Some experimental work has shown that the Vitamin D had a potent capacity to suppress TF expression, by tumor necrosis factor-α (TNFα, a key activator of TF) [26-29]. Other studies demonstrated a significant positive correlation between Vitamin D and TFPI levels [26], hence Vitamin D could exert anticoagulant effects.

An inflammatory phase

The next phase of wound healing is inflammation: the injured epithelial or endothelial cells release excessive inflammatory mediators, inducing the sequential infiltration of inflammatory cells (neutrophils, macrophages and lymphocytes). Macrophages can release cytokines IL-13, IL-1, growth factors such as active transforming growth factor β (TGF-β), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF) and TNF-α, which promote the inflammatory response and fibrosis [5, 30-33]. These intricate and poorly understood interactions ultimately result in myofibroblast activation and collagen expression, especially TGF-β, a multi-

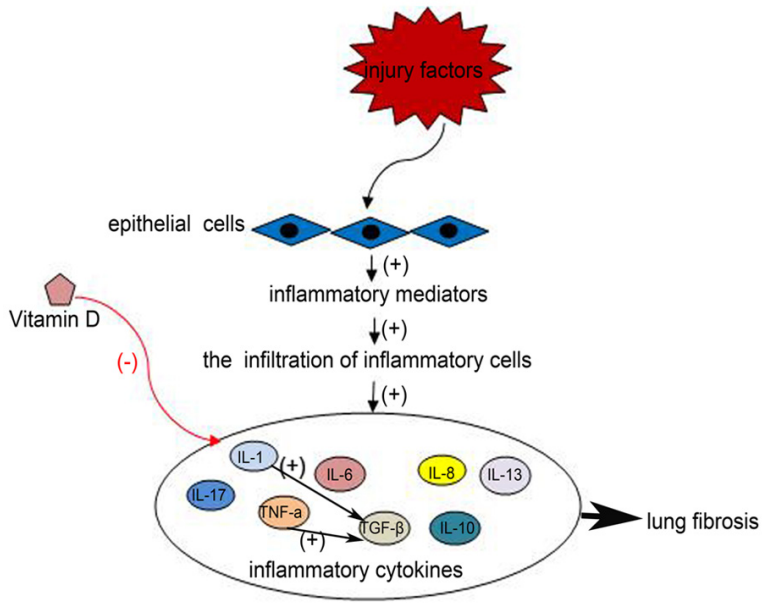

Figure 2. The injured epithelial cells release excessive inflammatory mediators, inducing the sequential infiltration of inflammatory cells. Then inflammatory cells release cytokines (IL-1, IL-6, IL-8, IL-10, IL-13, IL-17, TGF-β, TNF-α), which promote the inflammatory response and fibrosis. Vitamin D can reduce the levels of inflammatory cytokines, preventing the further expansion of the inflammatory response.

functional cytokine that is causally linked to pulmonary fibrosis.

Past research suggests that inflammatory mediators play a role in the initiation and progression of pulmonary fibrosis [34, 35]. However, now more studies are showing that pulmonary fibrosis is the consequence of multiple repeated injuries to the lung epithelium [5, 30]. The concept of pathogenesis for lung fibrosis has been transited inflammatory-driven into an epithelial-driven, and inflammation is not a cause, but a consequence, of pulmonary fibrosis [5, 30].

Vitamin D has been shown to cause decline in serum inflammatory cytokine levels (**Figure 2**), including IL-13 [36], IL-17 [36, 37], IL-1, IL-6, IL-8, and TNF-α [38], and may also act directly on CD4+ T cells to promote T-regulatory cells (Tregs) that secrete the anti-inflammatory cytokine IL-10 [36, 37, 39, 40], and prevent the further expansion of the inflammatory response.

Several studies have supported the notion that VD3 could markedly inhibit activation of TGF-β signaling pathways, diminish the up-regulation of fibronectin and collagen expression, and also inhibit the trans-differentiation of TGF-β1 and stimulated lung epithelial cells into myofibroblasts [41, 42], and we will elaborate on this in the next section.

Fibroblast migration/proliferation/activation phase

After the inflammation, the wound healing process enters the next phase, where fibroblast hyperplasia and exaggerated ECM deposition is initiated, and more than one mechanism is involved in the fibrosis process.

TGF-β/SMAD signaling pathways: At the very beginning of lung damage, the injured epithelial or endothelial cells release excessive inflammatory mediators that start an anti-fibrinolytic-coagulation cascade that triggers clotting and creates an interim ECM. Then it enters the next phase, characterized by a fibroblast migration/proliferation/activation phase, and myofibroblasts plays a significant role in this phase. Myofibroblasts are converted from a variety of sources including settled mesenchymal cells, bone marrow progenitors (also entitled fibrocytes). Epithelial cells go through epithelial-mesenchymal transition (EMT) [7]. EMT of epithelial cells is a major step toward pulmonary fibrosis, and TGF-β is an accepted activator of EMT, and also plays a central role in the proliferation, differentiation, and migration of cells [41, 43-46].

TGF-β expression can be induced by proinflammatory cytokines, such as IL-1β and TNF-α, and IL-1β triggers TGF-β gene expression by activating NF-B and AP-1 pathways [47]. TGF-β attaches to cell surface type I and II serine/threonine receptor kinases, leading to phosphorylation of SMAD2 and SMAD3, then the phosphorylation of receptor kinases released into the cytosol, and make up a complex with SMAD4. Followed by into the nucleus, the activated Smad complexes in conjunction with SMAD-binding elements within the genome to play its role, such

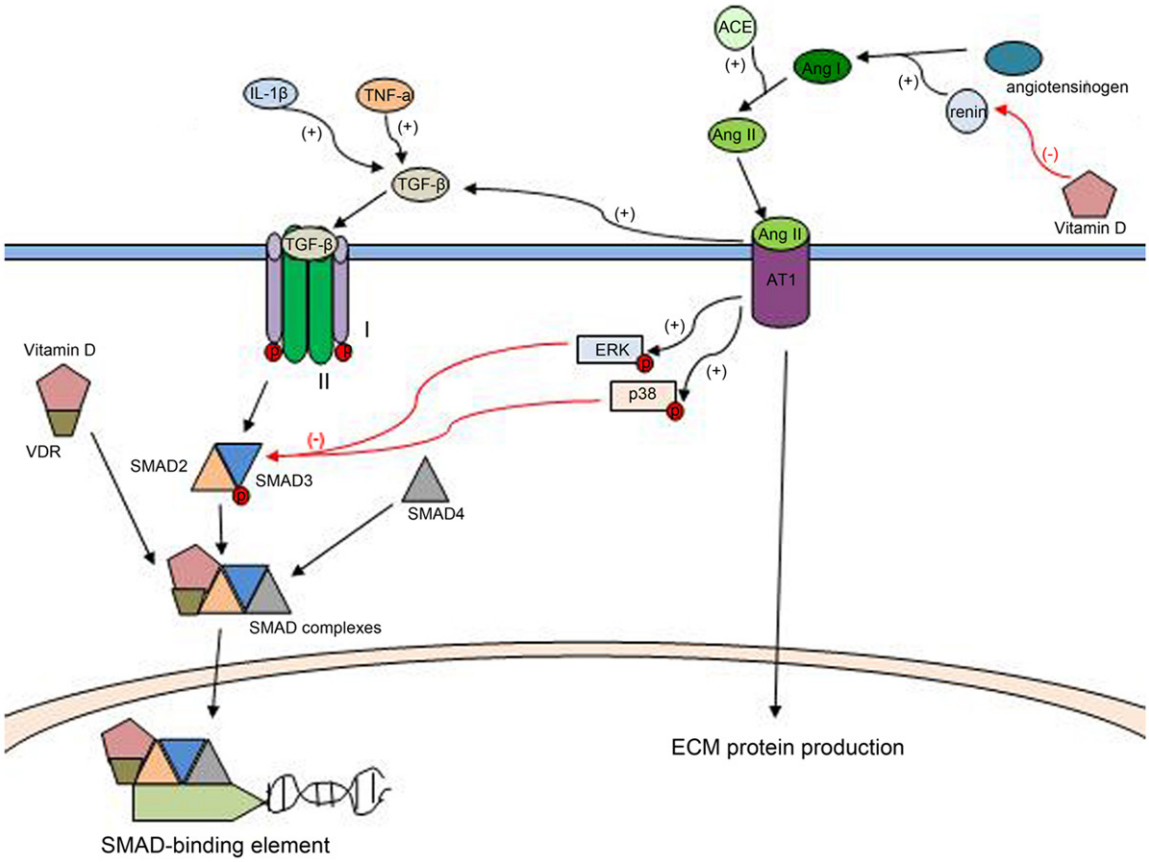

Figure 3. (1) TNF-α, and IL-1β can induce the expression of TGF-β. TGF-β attaches to cell surface type I and II serine/threonine receptor kinases, leading to phosphorylation of SMAD2 and SMAD3, then makes up a complex with SMAD4. Followed by translocation into the nucleus, the activated SMAD complexes in conjunction with SMAD-binding elements and plays its role. Vitamin D binds a complex with VDR, then the complex directly interacts with SMAD3 and decreases binding of SMAD3 to DNA, at last resulting in the inhibited TGF-β-SMAD signaling pathways. (2) Renin cleaves angiotensinogen to angiotensin (Ang) I, which is further converted to Ang II by ACE. Ang II plays an important role in lung fibrogenesis by the AT1 receptor. Ang II is activated by AT1 receptor, directly stimulates ECM protein production, and elevates the expression of TGF-β, meanwhile it activates SMAD2/3 directly by the ERK/p38 pathway. Vitamin D can reduce the expression of rennin, and regulate TGF-β SMAD3 signaling, Vitamin D causes negative regulation of the RASboth of these two ways.

as regulating the expression of profibrotics [48, 49].

Studies have revealed that Vitamin D can inhibits the TGF-β-SMAD signaling pathway [41, 50-52], and the details of this process is $1,25(OH)_2D_3$ binds a complex with VDR, then the complex directly interacts with SMAD3 and decreased binding of SMAD3 to DNA, at last resulting in the inhibited TGF-β-SMAD signal transduction [42, 53].

Ang II-AT1 receptor signaling: The activation of renin-angiotensin system (RAS) has been implicated to induce lung fibrosis both in transgenic animals and in disease models [54-56], and is recognized one important pathogenic factor in the pathogenesis of lung fibrosis [57]. However, the induction of lung fibrosis by RAS is not due to hypertension, although hypertension is an independent risk factor for lung fibrosis [58]. The RAS consists of angiotensinogen (AGT), an aspartyl protease such as renin or cathepsin D, angiotensin-converting enzyme (ACE). Renin cleaves angiotensinogen to angiotensin (Ang) I, which is further converted to Ang II by angiotensin-converting enzyme (ACE). Ang II plays an important role in lung fibrogenesis by both AT1 and AT2 receptors, which are mediated mainly by the AT1 receptor [57, 59, 60]. Ang II activated by AT1 receptor, directly stimulates ECM protein production, and expression of TGF-β and

connective tissue growth factor (CTGF) [61, 62], both of which could activate the fibrotic cascade and contribute to the development of lung fibrosis. Importantly, Ang II can activate SMAD2/3 directly by the ERK/p38 pathway [63] (64), and regulate TGF-β/SMAD3 signaling at multiple levels.

Vitamin D plays its antifibrotic role through a negative regulation of the RAS (**Figure 3**). Research has shown that hypovitaminosis D has been the other face of RAS activation [64], and VDR knockout mice caused the over-expression of renin, resulting in more angiotensinogen transformed into angiotensin II. In summary, vitamin D could reduce over-activation of RAS, causing an antifibrotic effect. Besides, $1,25(OH)_2D_3$ binds a complex with VDR, and the complex directly interacts with SMAD3, which restrains the ERK/p38 pathway. Vitamin D plays its negative regulation of the RAS both of these two ways.

Discussion

A large number of studies have displayed the prominent role Vitamin D has in fibrosis disease. Vitamin D affects the progress of clotting/coagulation phase, inflammation phase, and fibroblast migration/proliferation/activation phase of pulmonary fibrosis, in many ways, and then plays its antifibrotic role.

However, the progress of pulmonary fibrosis is complex and results from different factors. More importantly, a variety of pathways could be responsible for lung fibrosis, not only TGF-β/SMAD signaling and Ang II-AT1 receptor signaling, but also other ways, such as NF-κB signaling [65, 66], WNT and β-catenin signaling pathways [67], and so on; which limits the antifibrotic role of Vitamin D.

Nevertheless, the evidence reviewed in this paper indicates a crucial role of Vitamin D in lung fibrosis.

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Disclosure of conflict of interest

None.

Address correspondence to: Lipan Peng, Department of Gastrointestinal Surgery, Shandong Provincial Hospital Affiliated to Shandong University, Jinan 250000, Shandong, China. Tel: +86-150-53102101; E-mail: 15053102101@163.com

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