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Alveolar-Repairing Effect of 1α,25-Dihydroxyvitamin D3 on Chronic Obstructive Pulmonary Disease Mouse Model Based on Differentiation Inducing: Mini Review

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Abstract

Chronic Obstructive Pulmonary Disease (COPD) is the leading cause of death worldwide, but there is no drug to cure completely. We previously reported for the first time in the world the 1α,25-dihydroxyvitamin D3 can improve emphysema in animal COPD model. The aim of this mini review was to describe the effect of 1α,25-dihydroxyvitamin D3 on alveolar regeneration based on differentiation inducing, which we have found. Indicating the usefulness for 1α,25-dihydroxyvitamin D3 in a COPD mouse model that better reflects human medical conditions, 1α,25-dihydroxyvitamin D3 can be expected for drug candidate for novel therapy of COPD.

Keywords: Chronic obstructive pulmonary disease; 1α,25-dihydroxyvitamin D3; Pulmonary administration; Alveolar-regeneraztion

Abbreviations: AT-I cells: Type I Alveolar Epithelial Cells; AT-II cells: Type II Alveolar Epithelial Cells; COPD: Chronic Obstructive Pulmonary Disease; $1,25(OH)_2D_3$: 1α,25-Dihydroxyvitamin D3; RXR: Retinoid X Receptor; VDR: Vitamin D Receptor

Introduction

Chronic obstructive pulmonary disease (COPD) is a collective term for chronic bronchitis and emphysema, and is the leading cause of death worldwide. Most are caused by long-term inhalation of cigarette smoke, which leads destroying alveoli which has a function as a gas exchange site. And tissue have been losing elasticity and making breathing difficult. However, there is no drug to cure completely.

Vitamin D preparations are currently in clinical use in various diseases. However, in recent years, vitamin D deficiency has become widespread in COPD patients and has been reported to correlate with disease severity [1,2]. In addition, it is reported that COPD patients with vitamin D deficiency have a significantly lower forced vital capacity and more frequent exacerbation of disease than patients rich in vitamin D [3-5]. While the relationship between vitamin D and COPD has been suggested in this way, our research group have found out at first time in the world that 1α,25-dihydroxyvitamin D3 ($1,25(OH)_2D_3$) has an effect of improving emphysema based on differentiation inducing by pulmonary administration to COPD model mice [6,7].

In this mini-review, we will introduce the pulmonary emphysema-improving effect based on the differentiation induction of $1,25(OH)_2D_3$ that we found.

Differentiation-Inducing by 1α,25-Dihydroxyvitamin D3 on Alveolar Cells in Vitro

The alveoli, the site of gas exchange, consist of the alveolar space in which gas is retained and the alveolar epithelium surrounding it. Alveolar epithelium consists of type I alveolar epithelial (AT-I) cells and type II alveolar epithelial (AT-II) cells. AT-I cells form a blood-air barrier with the capillary endothelial cells and the basement membrane surrounding the alveoli, exchanging gas in the alveoli with gas in the blood. AT-II cells contain large amounts of lamellar bodies that release pulmonary surfactant extracellularly and form a coating layer of alveoli. Type II epithelial cells have been reported to differentiate into type I alveolar epithelial cells.

In addition, in recent years, the presence of alveolar epithelial type II progenitor cells capable of differentiating into type I and type II epithelial cells has been reported in human alveoli [8]. Differentiation of these progenitor cells into epithelial cells is important for regeneration of alveolar cells destroyed by COPD (Figure 1).
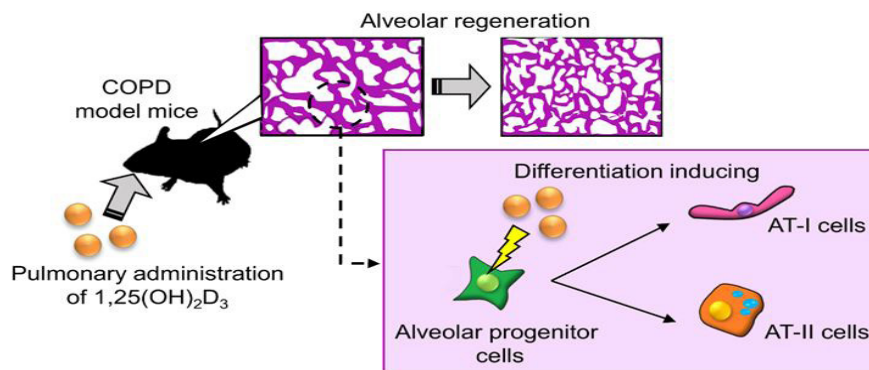

Figure 1: Concept of alveolar regeneration based on differentiation inducing. Pulmonary administered 1α,25-dihydroxyvitamin D3 into COPD model mice induce the differentiation of alveolar progenitor cells to the type I or II alveolar epithelial (AT-I or AT-II) cells in alveoli.

It has been clarified that a mesenchymal stem cell marker CD90 is expressed in human alveolar epithelial type II progenitor cells. Type I alveolar epithelial cells and type II alveolar epithelial cells are AQP-5 and SP-C positive as epithelial markers, respectively [8]. Our research group has found several drugs that can differentiate CD90-positive cells into alveolar epithelial marker-positive cells [9-11]. $1,25(OH)_2D_3$ can also induce cell differentiation [6]. The differentiation-inducing effects of $1,25(OH)_2D_3$ on cells has been previously reported for cancer cells such as leukemia cells and normal cells such as muscle cells [12,13]. Based on the results of precious studies, $1,25(OH)_2D_3$ is also expected as an alveolar differentiation inducer.

Emphysema Improving in COPD Model Mouse by Pulmonary Administration of 1α,25-Dihydroxyvitamin D3

Animal experiments for COPD emphysema are mainly conducted using mice and rats. COPD model animals are often produced by pulmonary administration of elastase to enzymatically destroy alveoli. It is considered that this is because the model is relatively easy to make including production period and the potential of drugs on the lungs can be easily determined. Our research group is also conducting evaluation using this model mouse [9,10,14,15]. As a result, pulmonary administration of $1,25(OH)_2D_3$ significantly reduced the mean liner intercept (distance between alveolar walls) of elastase-induced emphysema model mice, that means repaired alveoli, and improved respiratory function [6]. However, since this model mouse does not reflect the human pathological condition, it is considered necessary to evaluate the effect even in a model that better reflects human medical conditions. Previous studies reported that about 80% of patients in COPD had at least one additional comorbidity, about 55% had two or more comorbidities, and 35% had three or more comorbidities, which included arterial hypertension and so on [16]. In addition, another study reported that the prevalence of osteoporosis in COPD patients was higher than in healthy controls [17]. And most COPD patients are elderly, and there is concern that differentiation may be induced in an aging animal model.

Therefore, COPD model animals have been produced by various methods in order to better reflect the human pathological condition. Smoke-exposed animals showed physiological changes that mimic mild COPD in humans [18-23]. Furthermore, in the early period of smoke-exposure, it was found that the loss of exercise capacity, muscle wasting, and systemic inflammation [24,25]. Another research concluded that smoke-exposure in the guinea pig induces a transient and repeated oxidative effect, which might result in impaired systemic metabolism and consequent failure to gain weight [26]. However, the problem is that it usually takes about 6 months of smoke exposure to create the model, and severe emphysema cannot be reproduced [23]. Furthermore, in recent years, a number of model mice that have been genetically manipulated and reflect the COPD pathology have been developed. Among them, we focused on adiponectin. Adiponectin, which is a protein, is secreted by adipocytes [27]. In addition, it has been reported to decrease in patients with COPD, which strongly suggests its association with COPD pathology [28]. The adiponectin-deficient mouse is a COPD model mouse that exhibits not only aging emphysema but also systemic symptoms such as weight loss and bone loss [29]. In a previous study, we investigated the effect of $1,25(OH)_2D_3$ on emphysema-improving and systemic symptoms in adiponectin-deficient mice. Pulmonary administration of 0.1 μg/kg $1,25(OH)_2D_3$ to adiponectin-deficient mice twice a week for 30 weeks showed that the mean liner intercept was significantly reduced, and histologically improved emphysema. On the

other hand, with regard to systemic symptoms, changes in body weight and bone mass were examined, but $1,25(OH)_2D_3$ had no significant effect on these symptoms [7].

Typically, due to the high potency, use of the vitamin D analogs such as $1,25(OH)_2D_3$ is associated with a higher risk of hypercalcemia and hypercalciuria compared to native vitamin D supplementation [30,31]. However, in our study, most of the pulmonary administered $1,25(OH)_2D_3$ act on cells in the lungs, and the amount of drug that is systemically absorbed is low, so the risk of clinical concern is considered to be low. Pulmonary administration is a suitable administration method for diseases in which the lung is a lesion site such as emphysema because the drug can be directly delivered to the lung. In addition, previously study reported that intermittent dosing can reduce hypercalcemia rates [32]. However, the calcium level during long-term pulmonary administration is unknown, in the future, the assessment of the calcium level in blood and the $1,25(OH)_2D_3$ level in blood and tissue will help to better understand the effects of $1,25(OH)_2D_3$ on tissue.

Alveolar Repairing and Differentiation-Inducing Mechanism of 1α,25-Dihydroxyvitamin D3

Regarding the mechanism of differentiation inducing by $1,25(OH)_2D_3$, it has been reported from previous studies that it acts through Vitamin D receptor (VDR). It has been known a heterodimer is formed between VDR and retinoid X receptor (RXR) [33,34]. VDR deficient mice develop a COPD phenotype with increased expression of proinflammatory factors and matrix digesting enzymes [35]. In our studies, the increasing alveolar epithelial marker-positive cells with repair of the alveolar wall was observed in the lung tissue after pulmonary administration of $1,25(OH)_2D_3$, (data not shown). Therefore, it is highly possible that $1,25(OH)_2D_3$ acts on VDR in alveolar tissues. In addition, many signaling pathways involving VDR have been reported as below [36]. The deficiency of the VDR or $1,25(OH)_2D_3$ impaired the wound-healing response of the dermis to skin injury through reduced TGF-β signaling and SMAD3 phosphorylation [37]. A previous study reported a crosstalk between VDR and Stat1 signaling pathways, which affected $1,25(OH)_2D_3$-induced expression of VDR target genes in macrophages [38,39]. In another report, the association between β-catenin and the VDR in the nucleus can contribute to ligand-dependent transactivation, with β-catenin acting as a VDR coactivator [40]. β-catenin is an important downstream component of Wnt signaling, and in our previous studies, synthetic retinoid treatment suppressed Wnt gene expression during alveolar epithelial progenitor cell differentiation [10]. Furthermore, loss of the VDR leads to elevated c-MYC protein expression both *in vitro* and *in vivo* [41]. Appropriate regulation of c-MYC expression is also necessary for normal epidermal differentiation, and its overexpression leads to loss of epidermal stem cells [42-44]. Alveolar regeneration and differentiation-inducing mechanism of $1,25(OH)_2D_3$ is yet revealed. Therefore, it is expected that in the future, studies on gene expression of alveolar regeneration-related factors using microarrays and studies on the relationship between VDR agonist receptor activity and alveolar regeneration will be conducted.

Conclusion

$1,25(OH)_2D_3$ induced the differentiation of CD90 positive cells and the pulmonary administration of $1,25(OH)_2D_3$ is usefulness on COPD model mice. The effect of $1,25(OH)_2D_3$ on blood or tissue calcium levels and the alveolar-regeneration and differentiation mechanism and so on are yet unknown, and these evaluation on future study will help to better understand the usefulness of $1,25(OH)_2D_3$. On the other hand, $1,25(OH)_2D_3$ has an alveolar-repairing effect on adiponectin-deficient

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model mouse and was considered to be safe and is expected to have no adverse effect on systemic comorbidities. We believe that $1,25(OH)_2D_3$ to be a candidate for alveolar-regeneration drug based on differentiation inducing in COPD.

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