Review Article

PPARγ as a Potential Target to Treat Airway Mucus Hypersecretion in Chronic Airway Inflammatory Diseases

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Airway mucus hypersecretion (AMH) is a key pathophysiological feature of chronic airway inflammatory diseases such as bronchial asthma, cystic fibrosis, and chronic obstructive pulmonary disease. AMH contributes to the pathogenesis of chronic airway inflammatory diseases, and it is associated with reduced lung function and high rates of hospitalization and mortality. It has been suggested that AMH should be a target in the treatment of chronic airway inflammatory diseases. Recent evidence suggests that a key regulator of airway inflammation, hyperresponsiveness, and remodeling is peroxisome proliferator-activated receptor gamma (PPARγ), a ligand-activated transcription factor that regulates adipocyte differentiation and lipid metabolism. PPARγ is expressed in structural, immune, and inflammatory cells in the lung. PPARγ is involved in mucin production, and PPARγ agonists can inhibit mucin synthesis both *in vitro* and *in vivo*. These findings suggest that PPARγ is a novel target in the treatment of AMH and that further work on this transcription factor may lead to new therapies for chronic airway inflammatory diseases.

1. Introduction

Airway mucus hypersecretion (AMH) is a common pathological feature in chronic airway inflammatory diseases such as asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis (CF). Growing studies have suggested that AMH is associated with the progression of chronic airway inflammatory diseases and it is a significant contributor to morbidity and mortality. To control, AMH plays an important role in the treatment of chronic airway inflammatory diseases; however, effective therapies that target AMH are lacking [1, 2].

Peroxisome proliferator-activated receptors (PPARs) are a family of ligand-activated transcription factors belonging to the nuclear hormone receptor family. PPARs are related to retinoid, glucocorticoid, and thyroid hormone receptors [3]. They regulate diverse physiological processes, such as lipid biosynthesis and glucose metabolism, by binding to sequence-specific PPAR response elements in the promoter region of target genes. Recently, PPARs and their ligands have been found to inhibit the expression of proinflammatory genes, implicating them as regulators of immune and inflammatory responses. Several studies have demonstrated that PPAR ligands possess anti-inflammatory properties that may prove useful in the treatment of inflammatory lung diseases [4–6].

PPARγ is the most extensively studied PPAR subtype. It is involved in a series of lung diseases, including lung fibrosis, pulmonary vascular diseases, acute lung injury, and lung cancer [7–10]. Besides its regulatory role in adipocyte differentiation, glucose, and lipid metabolism, PPARγ activation reduces the synthesis and release of immunomodulatory cytokines from various cell types that participate in the regulation of inflammatory and immune processes. Specifically, mounting evidence suggests that PPARγ plays important roles in regulating processes related to airway inflammation, airway remodeling, and airway hyperresponsiveness, indicating that PPARγ and its ligand show potential as targets to develop treatments for chronic airway inflammatory diseases [11]. In fact, PPARγ has been implicated in AMH. Recent studies have shown that chronic airway inflammatory diseases in humans are associated with altered PPARγ

expression and that PPARγ ligand can attenuate AMH in both *in vitro* and *in vivo* experimental models. This paper will summarize recent work implicating PPARγ in AMH.

2. AMH and Chronic Airway Inflammatory Diseases

2.1. Significance of AMH. Mucus secretion is essential for protecting airways. It is vital for air humidification, warming, and cleaning [12]. However, in patients with chronic airway inflammatory diseases, excessive mucus is secreted into the airway, which leads to hospitalization and death in many patients. This hypersecretion, termed AMH, obstructs the airways, limits airflow, impairs gas change, and causes ventilation-perfusion mismatch. Patients with chronic airway inflammatory diseases that also present with AMH generally have poor lung function and high rates of hospitalization and death. Compromised mucociliary function can reduce mucus clearance, which can encourage bacterial colonization, leading to chronic pulmonary infections and exacerbations. In addition, chemicals synthesized by bacteria or released when bacteria are degraded by the immune system can stimulate mucin synthesis and mucus secretion, resulting in a vicious circle [1, 13].

Studies suggest that AMH is not merely a clinical symptom but instead a critical factor in the pathogenesis of chronic airway inflammatory diseases. AMH is associated with greater susceptibility to COPD, a decline in forced expiratory volume in one second, hospitalization, and excess mortality [14–16]. The incidence of COPD in young adults presenting with AMH symptoms is three-fold higher than that in subjects who have never reported AMH symptoms, regardless of their smoking habits [17]. These findings are supported by an analysis of the Framingham offspring cohort studies [18].

AMH has long been recognized as a major cause of death in asthma. One study found luminal occlusions covering 20–100% of the cross-sectional area in patients who died from asthma, leading the authors to conclude that luminal obstruction of airways by an exudate composed of mucus and cells is a major contributor to asthma fatality [19]. In addition, AMH symptoms such as chronic cough or phlegm are independently and significantly related to uncontrolled asthma, and a history of persistent symptoms related to AMH is associated with a more severe asthma phenotype [20]. AMH also contributes to morbidity due to cystic fibrosis (CF). In CF patients, the reduced ability of epithelial cells to secrete chloride usually leads to reduced mucus accumulation in the airways, which favors chronic infection by *Pseudomonas aeruginosa* and other organisms. AMH contributes to CF morbidity by increasing the frequency and severity of pulmonary infections as well as by impairing lung function [21].

2.2. Inflammation and AMH. Abnormal inflammatory response is the major component of chronic airway inflammatory diseases. Such inflammatory response has been associated with AMH in airway diseases. Numerous studies have demonstrated that inflammatory stimuli and mediators/cytokines contribute to excess mucin synthesis and mucus secretion in airways. For instance, cigarette smoke, neutrophil elastase, and *P. aeruginosa* proteases are well-known inflammatory stimuli that can cause significant inflammatory responses, which result in goblet cell metaplasia and hyperplasia, leading in turn to mucin overproduction and mucus hypersecretion in airways [22–24]. Inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, IL-6, IL-8, IL-13, and IL-17 can upregulate the expression of MUC5AC, the marker of goblet cell metaplasia, through different signaling pathways [25–29]. This is the most important event in the pathogenesis of AMH. Thus, the ability to control airway inflammatory responses should reduce AMH and thereby benefit patients with chronic airway inflammatory diseases. However, current anti-inflammatory treatments with corticosteroids are not effective in all patients with chronic airway inflammatory diseases. Thus, the search for novel drug targets for these diseases continues.

In summary, AMH arising as a result of inflammatory processes can lead to physiologically and clinically measurable mechanical airway obstruction in patients with chronic airway inflammatory diseases. In this way, AMH significantly affects the pathogenesis, progression, and prognosis of these diseases. Therapies that aim to control the inflammation that triggers AMH may be effective at treating chronic airway inflammatory diseases [30–32].

3. Expression and Anti-Inflammatory Role of PPARγ in the Lung

3.1. Expression of PPARγ in Lung Cells. PPARγ is expressed in many types of structural cells in the lung, including fibroblasts, ciliated airway epithelial cells, alveolar type II pneumocytes, and airway smooth muscle cells [3, 4, 32]. A study in PPARγ-knockout mice has highlighted the role of this transcription factor in animal models. A specific PPARγ deletion in airway epithelium produced persistent enlargement of the airspaces in adult mice, which showed more severe emphysema symptoms and higher macrophage numbers after exposure to cigarette smoke than did mice carrying the PPARγ gene [33]. These results suggest that epithelial PPARγ is required for proper lung maturation and response to injury.

PPARγ is also present in several types of inflammatory, immune cells in the lung, where it exerts anti-inflammatory and immuno-modulatory effects. Specially, PPARγ has been found in macrophages, eosinophils, T cells, B cells, and dendritic cells [34–38]. It plays an anti-inflammatory role in lung cells mainly by inhibiting cytokine production and enhancing phagocytosis of apoptotic neutrophils, a process essential to resolve inflammation.

Increasing evidence suggests that altered PPARγ expression and function may be associated with chronic airway inflammatory diseases and that stimulation of this receptor may attenuate inflammatory responses. A study examining the expression of PPARγ in lung tissues of patients with COPD found the protein to be present mainly in alveolar

epithelial cells and smooth muscle cells in the bronchial walls. The intensity of PPARγ was inversely proportional to the severity of the COPD, with the signal stronger in patients with milder COPD [39]. Another study found that PPARγ is expressed in CF- and non-CF-type human airway epithelial cells, but appears to be either less abundant, less functional in binding its target DNA sequence, or both, in CF [40]. In asthmatic individuals, but not healthy objects, segmental allergen challenge led to downregulation of PPARγ mRNA and protein expression in alveolar macrophages [41]. These findings are suggestive of a role for PPARγ agonists in the treatment of chronic lung inflammatory diseases.

3.2. The Anti-Inflammatory Role of PPARγ. Building on the evidence linking PPARγ and airway inflammatory diseases, several studies have investigated the therapeutic role of the receptor and its ligand in cellular and animal models of these diseases. Administration of PPARγ ligand to BALB/c mice sensitized and challenged with ovalbumin (OVA) reduced the levels of proinflammatory mediators in bronchoalveolar lavage fluid (BALF) and attenuated the inflammatory response in the lung [35, 42, 43]. Treating human airway epithelial cell line A549 with the PPARγ agonist troglitazone blocked the ability of phorbol 12-myristate 13-acetate to stimulate an increase in TNF-α levels. However, this effect of troglitazone required the presence of MUC1/Muc1 [44]. The authors concluded that PPARγ exerts an anti-inflammatory effect by stimulating MUC1/Muc1 expression, which then blocks the production of TNF-α/IL-8 induced by phorbol 12-myristate 13-acetate in airway epithelial cells [44]. In addition, PPARγ plays an essential role in the pathway through which monocyte/macrophage-derived microparticles activate NF-κB and ultimately induce upregulation of proinflammatory mediators in human lung epithelial cells [45].

The anti-inflammatory effect of PPARγ is thought to be due mainly to its ability to downregulate proinflammatory gene expression. It does so by sequestering shared coactivators, reducing the ability of inflammatory transcription factors to bind their target DNA. The second way is through ligand-dependent transrepression, preventing other transcription factors' association with DNA sequences. At the same time, PPARγ can increase the transcription of anti-inflammatory genes. Agonist binding to PPARγ induces a conformational change in the receptor, allowing the dissociation of corepressors and the association of coactivator molecules. This allows the formation of PPARγ dimmers or heterodimers and subsequent interaction with peroxisome proliferator response elements, which increases anti-inflammatory gene transcription [46].

Taken together, these findings suggest that PPARγ participates in both physiological and pathological processes in chronic airway inflammatory diseases. These studies make a strong case for PPARγ activation as a potential treatment for chronic airway inflammatory diseases.

4. PPARγ and AMH

Since the inflammatory response is the major contributor to AMH, and PPARγ and its ligand help regulate airway inflammation, several studies have investigated the potential involvement of PPARγ and its ligand in AMH.

Lee and colleagues carried out the first study to examine the role of PPARγ ligand on mucin production in human airway epithelial NCI-H292 cells exposed to cigarette smoke [47]. Exposure caused a significant increase in TNF-α and MUC5AC production, which was attenuated by administration of the PPARγ agonist rosiglitazone. Rosiglitazone increased the expression of phosphatase and tensin homolog deleted on chromosome 10 (PTEN) and inhibited the PI3K/Akt pathway. PTEN antagonizes PI3K-mediated signaling, whose role in mucin production is well documented [47, 48]. These results provide the first evidence that a treatment targeting PPARγ can significantly inhibit cigarette smoke-induced mucin production, raising the possibility that this approach may be useful in the clinic. Indeed, the study authors proposed that using a PPARγ agonist to activate PTEN and inhibit PI3K/Akt may be a potential therapy for cigarette smoke-induced mucin secretory diseases [47].

Subsequent studies evaluated the effect of rosiglitazone on airway mucin production in animal models of AMH. Exposing rats for two weeks to acrolein, one of the most toxic components in cigarette smoke, induced goblet cell hyperplasia in bronchial epithelium and upregulated MUC5AC mRNA and protein expression in rat lungs. These changes were associated with airway inflammation, as evidenced by the increased numbers of inflammatory cells and levels of inflammatory cytokines (IL-1β, IL-8, and TNF-α) in BALF. Treating the rats with rosiglitazone before acrolein exposure attenuated these changes in a dose-dependent manner [49]. Rosiglitazone has also been shown to inhibit NF-κB activation, which is well known to play an important role in regulating not only multiple inflammatory cytokines but also AMH in inflammatory lung diseases [50, 51]. Therefore, inhibition of NF-κB activation by rosiglitazone may explain the observed downregulation of proinflammatory mediators and the reduction in AMH. From these findings, Liu et al. concluded that ligand-induced activation of PPARγ may be a novel therapy for AMH in chronic airway inflammatory diseases such as COPD [49].

AMH is also an important pathologic feature of asthma, which is characterized by nonspecific airway inflammation. Several studies have examined the involvement of PPARγ and its ligand on AMH in a mouse model of asthma. AMH was observed in airways of animals sensitized and challenged with OVA, while it was barely detectable in airways of nonsensitized animals. Administration of the PPARγ agonist ciglitazone via nebulizer reduced OVA-induced mucus gland hyperplasia and airway occlusion due to mucus hypersecretion by approximately 75% [52]. In a different mouse model, mice were exposed or not to toluene diisocyanate to induce asthma. Exposed mice that received PPARγ agonists (rosiglitazone or pioglitazone) or adenovirus carrying PPARγ2 cDNA showed a lower percentage of airway epithelium staining positive with PAS than did exposed mice that did not receive agonists or adenovirus [53]. In addition, both of these studies found that PPARγ agonists support protective remodeling of the airway wall by regulating TGF-β or TGF-β1 and collagen deposition. Results from both of

these mouse models support the possibility of using PPARγ agonist to treat AMH in humans.

In addition to these observations in cell lines or animal models, several lines of indirect evidence link activation of PPARγ and AMH. Activation of PPARγ by rosiglitazone or pioglitazone markedly reduced mRNA expression of matrix metalloproteinase-9 (MMP-9) and inhibited TNF-α induced MMP-9 gelatinolytic activity [54]. Since MMP-9 is an important MMP related to AMH [55], these results suggest that PPARγ may attenuate AMH through a pathway involving MMP-9. Simvastatin is a statin that modulates inflammatory processes and that can inhibit mucin production and AMH [56]. A recent study indicated that its anti-inflammatory effect may involve PPARγ activation [57], which means that simvastatin may suppress AMH via a mechanism mediated by PPARγ. It seems clear from these diverse lines of evidence that the effects of PPARγ and its ligand on AMH are mediated by multiple mechanisms. Further work is needed to identify new ligands of PPARγ and investigate the signaling pathways affected by the receptor.

In summary, substantial evidences indicate that PPARγ is involved in AMH and that PPARγ ligand suppresses AMH by inhibiting proinflammatory cytokines and inflammatory signaling pathways. Therefore, PPARγ agonists may have potential as treatments for AMH in chronic airway inflammatory diseases.

5. Considerations for Targeting PPARγ in the Treatment of AMH

Although several studies have suggested that PPARγ is involved in AMH and that PPARγ agonists inhibit AMH, there is still a long road ahead before laboratory studies can be translated to the clinic. For one thing, the pathogenesis of chronic airway inflammatory diseases such as COPD, asthma, and CF is extremely complicated. Only a few studies, most of them descriptive, have directly investigated the role of PPARγ and PPARγ ligand in AMH. As a result, the signaling pathways affected by PPARγ or PPARγ agonists remain poorly understood. Further investigation of these areas will be required to define the effects of PPARγ ligands on airway epithelial cells and the mechanisms by which these pro- and/or anti-inflammatory responses occur.

A second consideration for targeting PPARγ in the clinic is that the route of PPARγ agonist administration may be important. In Honda's study [52], treating Balb/c mice with nebulized ciglitazone led to a reduction in mucus production in the airways, whereas orally administered ciglitazone had no such effect [58]. Oral gavage of rosiglitazone or pioglitazone reduced toluene diisocyanate-induced AMH in Balb/c mice [53], while oral rosiglitazone treatment had no effect on goblet cell hyperplasia in C57BL/6 mice [59]. Future work should clarify whether the different results observed with different agonists or models of administration reflect differences in the sensitivity of mouse strains to regulation of airway inflammation and AMH, or whether agonist identity and mode of administration are crucial.

Finally, the safety of PPARγ agonists in patients with chronic airway inflammatory disease should be carefully examined. Recent studies suggest an association between rosiglitazone treatment and increased risk of cardiovascular events in patients with type 2 diabetes [60, 61]. Thus it remains to be seen whether PPARγ agonist is safe for patients with chronic airway inflammatory diseases.

6. Summary

The present paper describes the clinical importance of AMH in the pathogenesis of chronic airway inflammatory diseases and makes the case for exploring PPARγ and PPARγ ligand as potential target in treating AMH. Corticosteroid is the first-line anti-inflammatory drug used to chronic airway inflammatory diseases, but its therapeutic effects are controversial, and physicians have begun to pay attention to its undesirable side effects [62]. In fact, it is generally accepted that steroids have only limited effects on AMH [63], so there is a demand for novel and effective anti-inflammatory drugs that can reduce AMH. Increasing evidence suggests that PPARγ is involved in mucin production and that PPARγ agonists inhibit AMH both *in vitro* and *in vivo*. Indeed, a recent clinical trial found that rosiglitazone improved lung function in steroid-resistant asthma patients [64], providing direct evidence that patients with chronic airway inflammatory diseases can benefit from PPARγ agonist treatment. Thus, PPARγ agonists may represent a novel class of pharmacological agents useful in the management of AMH in chronic airway inflammatory diseases.

Acknowledgments

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