**PEROXISOME PROLIFERATOR-ACTIVATED RECEPTORS**

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**Abstract**

Peroxisome proliferator-activated receptors (PPARs) are members of the ligand-activated nuclear hormone receptor superfamily of transcription factors that includes receptors for steroids, thyroid hormone, retinoic acid, and vitamin D. Upon activation in the cytoplasm, PPARs heterodimerize with retinoid X receptors (RXR) and form a complex that translocates to the nucleus and regulates gene expression. PPARs are thought to play roles in diverse physiological processes ranging from lipid metabolism to inflammation, and have been implicated in diseases such as cancer, atherosclerosis, and diabetes. Although information about the function of PPARs in lung is scarce, data

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**Glossary**

ELF – epithelial lining fluid. Attenuated layer of fluid which covers the epithelial surface

BAL – bronchoalveolar lavage. Lungs are lavaged with saline to recover cellular, microbial, and solute constituents of ELF

EBC – exhaled breath condensate

Aquaporins – water channels in cell membranes

**Nomenclature**

\[ J_V \] flow of fluid across the membrane (e.g., \( \text{ml min}^{-1} \))

\[ K_f \] filtration coefficient, e.g., \((\text{ml min}^{-1})/(\text{mmHg difference} \times \text{cm}^2/\text{surface area})\)

\( S \) surface area of membrane

\( \sigma \) index of leakiness of membrane to solute (dimensionless). If \( \sigma = 1 \), no leakage occurs; if \( \sigma = 0 \), then the solute readily leaks across the membrane and can exert no osmotic pressure

\( \Delta D \) hydrostatic pressure difference across the membrane (e.g., \( \text{mmHg} \))

\( \Delta \pi \) osmotic pressure which would be exerted by the concentration difference of a solute across the membrane if the membrane were completely impermeable to the solute
Implicating these molecules in key processes in lung biology are rapidly emerging. In lung, PPARs are expressed by recruited immune cells (e.g., monocytes) and in resident cells such as tissue macrophages, bronchial and alveolar epithelial cells, endothelium, and airway smooth muscle, among other cell types. Of the three PPAR forms (PPAR-α, PPAR-β/δ, PPAR-γ), PPAR-γ is the best studied, and it is believed to regulate cellular differentiation and proliferation. Several studies suggest that PPAR-γ serves to downregulate lung inflammation, promotes vascular function, and acts as a tumor suppressor in lung and other carcinomas.

Introduction

Since their discovery in 1990, peroxisome proliferator-activated receptors (PPARs) have captured the attention of investigators interested in learning about the intracellular pathways that control signal transduction and gene transcription. PPARs were originally cloned in an attempt to identify the molecular mediators of peroxisome proliferation in the liver of rodents. Today, PPARs are recognized as versatile members of the ligand-activated nuclear hormone receptor superfamily of transcription factors that includes receptors for steroids, thyroid hormone, retinoic acid, and vitamin D. PPARs are considered to play key roles in diverse physiological processes ranging from lipid metabolism to inflammation, and have been implicated in diseases such as cancer, atherosclerosis, and diabetes. Although information about the function of PPARs in lung is scarce, data implicating these molecules in key processes in lung biology are rapidly emerging.

PPARs are characterized by three functional domains: the N-terminal domain (a site for functional regulation by phosphorylation), the DNA-binding domain, and the ligand-binding domain. Upon activation in the cytoplasm, PPARs heterodimerize with retinoic X receptors (RXR) and form a complex that translocates to the nucleus and regulates gene expression (Figure 1). Ligand binding to PPARs appears to trigger conformational changes that permit their dissociation from co-repressors and favor their association with coactivators (e.g., steroid receptor coactivator-1 and p300). The heterodimer–coactivator complex binds to specific response elements (termed PPREs) in the promoter regions of target genes that consist of a direct repetition of the consensus A-G-T-C-A half site spaced by one or two nucleotides (DR1 or DR2) (Figure 1A). The coactivator proteins possess or recruit histone acetyltransferase activity to the transcription start site. Acetylation of histone proteins alters chromatin structure, facilitating the binding of RNA polymerase and the initiation of transcription. In addition to their stimulatory effects on gene transcription, PPARs can repress gene expression in a DNA-binding-dependent manner through the recruitment of co-repressors to

![Figure 1](image-url)
unliganded PPARs (Figure 1B) or in a DNA-binding-independent manner by interfering with key transcription factors (Figure 1C).

Three subtypes of PPARs have been identified and cloned: PPAR-α, PPAR-β/δ, and PPAR-γ. These subtypes are distinguished by their tissue distribution, and to a lesser degree, by their ligand specificity. Most studies defining the role of PPARs in lung structure and function have examined PPAR-γ. Therefore, for the most part, this review focuses on the role of PPAR-γ in lung health and disease.

PPARs are activated by structurally diverse ligands. PPAR-γ is activated by the synthetic thiazolidinedione (TZD) class of insulin-sensitizing agents such as troglitazone, rosiglitazone, and pioglitazone, and certain nonsteroidal anti-inflammatory drugs (e.g., indomethacin, ibuprofen, fenoprofen, flufenamic acid). Natural ligands for PPAR-γ include prostanoids, prostaglandin D2, 15-deoxy-A12,14-prostaglandin J2 (15d-PGJ2), and certain polyunsaturated fatty acids. These reagents have been used to elucidate the role of PPAR-γ in cellular functions both in vitro and in vivo. However, several caveats should be taken into consideration when interpreting such studies. First, the natural ligands that regulate PPARs in vivo have not been determined. Second, not all PPAR-γ ligands exert their effects through PPAR-γ since there is strong evidence for the activation of PPAR-γ-independent signals, particularly with the natural ligand 15d-PGJ2. Third, high affinity ligands for PPAR-γ (e.g., the TZDs) may exert partial agonist/antagonist activity. The latter might be due to the fact that individual TZDs induce different PPAR-γ conformations that influence the recruitment of different coactivator/co-repressor molecules. Thus, the activity of the PPAR-γ transcriptional complex is influenced by the context of a given gene and its promoter, and by the relative availability of pertinent coactivator/co-repressor molecules in the cell or tissue of interest.

**PPARs in Lung**

In lung, PPARs are expressed by recruited immune cells (e.g., monocytes) and in resident cells such as tissue macrophages, bronchial and alveolar epithelial cells, endothelium, and airway smooth muscle, among other cell types. In developing murine lungs, PPAR-γ expression was found to increase as the lung matured. Although the exact roles PPAR-γ and other PPARs play in fetal and adult lungs are unknown, their wide distribution and their ability to regulate cellular proliferation and differentiation as well as apoptosis in vitro suggest important functions for PPARs in lung homeostasis. The factors that regulate PPAR expression in lung also remain unelucidated. In this regard, it has been reported that agents known for their ability to stimulate alveolar epithelial type II cell differentiation (e.g., dexamethasone, retinoic acid, cAMP, growth factors) stimulate PPAR-γ expression (Figure 2).

Several studies performed in lung tissues and in isolated primary lung cells have begun to unveil potential roles for PPARs in lung including surfactant homeostasis. Specifically, it was found that 15d-PGJ2 and 9-hydroxyoctadecanoic acid upregulate PPAR-γ and downregulate surfactant protein B expression in cultured cells and in fetal lung explants. In other work, PPAR-γ agonists were shown to inhibit elastin production and z-smooth muscle actin expression in fibroblasts, which suggests a role in myofibroblast differentiation. In cultured bronchial epithelial cells, PPAR-γ agonists exert antiproliferative effects and inhibit the expression of matrix metalloproteinase-9. In human airway smooth muscle cells, PPAR-γ agonists inhibit proliferation induced by several stimulants. This and other information discussed below suggest that, at baseline, PPARs might help maintain homeostasis by inhibiting inflammation, and perhaps tissue remodeling, and that their downregulation might predispose to disease. This is consistent with data showing decreased PPAR-γ expression in the alveolar macrophages of humans with alveolar proteinosis and in the vascular lesions of subjects with pulmonary hypertension.

**PPARs, Airways, and Modulation of Inflammation**

Despite their demonstrated role in cellular proliferation and differentiation, it is the anti-inflammatory activities of PPARs that have attracted much attention. Using a model of paw edema induced by subplantar injection of carrageenan, it was found that rosiglitazone inhibited the edema in a dose-dependent fashion. Rosiglitazone also attenuated polymorphonuclear cell infiltration of the pleural cavity, neutrophil infiltration of lung tissue, and lipid peroxidation after injection of carrageenan into the pleura. A general exploration of the potential pathways involved in these effects revealed decreased tissue staining for intercellular adhesion molecule-1 and p-selectin, which could explain the reduction in immune cell recruitment into the lung. Reductions in nitric oxide levels and the activity of inducible nitric oxide synthase, and decreases in levels of tumor necrosis factor alpha and interleukin-1β were also detected. PPAR-γ agonists have also been shown to ameliorate airway neutrophilia and the associated expression of chemoattractants in animals exposed to aerosolized endotoxin.

The documentation of the anti-inflammatory effects of PPAR-γ ligands has led to investigations testing
their potential role in experimental models of asthma. In a murine model of asthma induced by sensitization and airway challenge with ovalbumin, PPAR-γ was found to be expressed mainly in airway epithelium after antigen sensitization. The PPAR-γ agonist ciglitazone (administered by nebulization or by means of gavage) decreased airway hyperresponsiveness, basement membrane thickness, mucus production, collagen deposition, and transforming growth factor beta-1 synthesis. PPAR-γ agonists were also shown to decrease the proliferation of antigen-specific T cells and to increase the production of the immunomodulatory cytokine interleukin-10.

These and other studies suggest that PPARs, especially PPAR-γ, exert anti-inflammatory roles in lung and other organs. As such, their activation might serve to counter inflammatory responses induced by injury, and their dysregulation might promote uncontrolled tissue damage due to unopposed inflammation and, perhaps, tissue remodeling. Prolonged leukotriene B4-induced inflammatory responses in PPAR-α-deficient mice suggest potential anti-inflammatory roles for PPAR-α as well. How PPAR agonists inhibit inflammation is the subject of intense investigation. Mounting evidence indicates that PPAR-γ inhibits the expression of proinflammatory mediators through effects on potent transcription factors such as nuclear factor kappa B (NF-κB), STAT1, and activation protein-1 (AP-1). Similar observations have been made for the transcription factors Smad3 and CREB element binding protein (CREB).

**PPARs in the Lung Vasculature**

Several studies point to a potential protective role for TZDs in vascular disease and suggest that PPAR-γ activation in the vascular wall has predominantly antiatherogenic effects. These studies are supported by limited *in vivo* data in animal and human subjects indicating that TZD therapy is associated with improved endothelial function. However, the role of PPARs in the pulmonary vasculature remains to be defined. The abundance of immunoreactive PPAR-γ has been found to be greater in type II epithelial cells than in type I epithelial cells, bronchial epithelial cells, or endothelial cells in the lung. However, despite relatively lower expression of PPAR-γ in endothelial compared to epithelial cell compartments, the anti-inflammatory effects of PPAR-γ activation appear to extend into the vasculature. In the rat model of sepsis induced by cecal ligation and perforation, treatment with the PPAR-γ ligands 15d-PGJ2 or ciglitazone reduced sepsis-mediated hypotension, vascular injury, and pulmonary neutrophil infiltration and resulted in significant improvements in survival. In this study, PPAR-γ ligands attenuated sepsis-induced...
reductions in lung PPAR-γ expression and reduced markers of vascular inflammation including nitrotyrosine staining and poly(ADP-ribose) synthetase activation in thoracic aorta, although the relative contributions of pulmonary versus systemic vascular effects of PPAR-γ activation were not defined. Other studies have demonstrated that PPAR-γ ligands attenuate vascular injury and dysfunction in zymosan-induced sepsis and in ischemia–reperfusion-related lung injury. The role of PPAR-α or -δ in the regulation of pulmonary vascular responses has not been examined.

Based on the ability of PPAR-γ to regulate vascular smooth muscle cell migration and proliferation, apoptosis, and angiogenesis, several investigators examined PPAR-γ expression in lung tissue from patients with primary and secondary forms of pulmonary hypertension and from normal lung tissue. PPAR-γ expression was evident in alveolar wall structures and small vessel endothelium in normal lung, and its expression was attenuated in these structures from patients with pulmonary hypertension. Interestingly, PPAR-γ expression was also reduced in the complex vascular lesions comprised of proliferating endothelial cells in an experimental rat model of pulmonary hypertension. In ECV304 cells, a human endothelial-like cell line, shear stress decreased PPAR-γ expression suggesting that altered blood flow in hypertensive pulmonary vessels could account for reduced PPAR-γ expression and the proliferative endothelial lesions in this disease. Supporting this concept were additional data that overexpression of PPAR-γ in ECV304 cells reduced, while dominant-negative PPAR-γ enhanced, the in vitro angiogenic potential of this endothelial cell line. Although a causal relationship between reduced PPAR-γ and endothelial proliferation, vascular obstruction, and pulmonary hypertension remains to be established, recent evidence that PPAR-γ activation stimulates endothelial nitric oxide release provides additional potential mechanistic links between PPAR-γ and pulmonary hypertension.

Several studies have implicated PPAR-γ in lung cancer as well. PPAR-γ is expressed in small cell and non-small cell lung carcinomas (NSCLC), and PPAR-γ agonists induce growth arrest and induce changes associated with differentiation as well as apoptosis in a variety of lung carcinoma cell lines. For example, PPAR-γ agonists have been found to inhibit the growth of A549 adenocarcinoma cells due to G0/G1 cell-cycle arrest through the downregulation of G1 cyclins D and E; this was related to sustained Erk 1/2 activation. Most notably, the treatment of NSCLC tumor-bearing SCID mice with a PPAR-γ ligand inhibited tumor growth and metastasis. PPAR-γ agonists have also been shown to inhibit lung carcinoma cell proliferation through inhibition of cyclooxygenase-2 and reduction in the expression of prostaglandin E2 receptors. In primary NSCLC, the expression of PPAR-γ was correlated with tumor histological type and grade, and decreased PPAR-γ expression was correlated with poor prognosis. Thus, it has been postulated that PPAR-γ mRNA levels may serve as a prognostic marker in lung carcinoma in addition to playing important roles in lung carcinogenesis. However, the first clinical trials to make use of the antineoplastic effects mediated by PPAR-γ have shown conflicting results.

In summary, although their exact role in lung remains undefined, PPARs are believed to regulate cellular differentiation and proliferation, and studies performed with agonists of PPAR-γ, the best studied of the PPARs, suggest that this form of PPAR serves to downregulate lung inflammation, promotes vascular function, and acts as a tumor suppressor in lung carcinomas. The availability of PPAR-γ agonists in the clinical arena will aid in investigations directed at studying the true role of PPARs in lung health and disease.

See also: Lipid Mediators: Overview; Prostanoids. Smooth Muscle Cells: Vasculaer. Transcription Factors: NF-κB and IκB.

Further Reading


**PHYSIOTHERAPY**

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**Abstract**

Physiotherapy has long been utilized in the treatment of patients with respiratory problems. In the late 1950s, breathing exercises were recommended as a treatment for patients with chronic chest diseases but this suggestion was short-lived, as the efficacy of these exercises was inconclusive. Until the late 1970s, chest physiotherapy was a passive treatment on the part of the patient and the physiotherapist carried out manual chest physiotherapy techniques including percussion, vibrations, and shaking with gravity-assisted positions. The development of the active cycle of breathing technique (breathing control, lower thoracic expansion exercises, and forced expiratory technique), autogenic drainage, and adjunct physiotherapy aids in the removal of secretions. Procedures such as intermittent positive breathing techniques, have enhanced the treatment of chest clearance for patients with acute or chronic respiratory problems. Chest physiotherapy is routinely employed as a prophylactic measure prior to major surgery and postoperatively to prevent respiratory complications such as atelectasis and pneumonia. However, most of the systematic reviews that examined these techniques were inconclusive in their findings. To ascertain the benefits of these techniques in terms of reducing respiratory morbidity and healthcare usage and to improve the quality of life for patients with chronic respiratory problems, well-controlled clinical trials are needed.

**Introduction**

Respiratory disease has a substantial impact on the health of the population at all ages and every level of morbidity. Acute upper respiratory tract infections, including chronic lung diseases, are common causes of visits to general practitioners; they are a common cause of hospital admissions during the winter months, particularly in the elderly.

Physiotherapy is the art and science of utilizing a variety of modalities to treat by using hands in order to maximize physical function. Chest physiotherapy assists the clearance of secretions and reduces breathlessness to improve lung function and reduce morbidity and mortality. Excessive bronchial secretion retention may contribute to the development of symptoms such as airflow obstruction, wheeze, shortness of breath, fatigue, and cough.

Chest physiotherapy is defined as a combination of several mucus-clearance techniques to treat patients with acute or chronic respiratory problems by assisting mucus transport in order to improve lung function. These techniques can be used in a hospital ward setting, either in isolation or with mechanical devices, to treat patients with acute exacerbations, including those on life support machines in critical situations in the intensive care unit.

Impaired clearance of the airways may lead to the development of respiratory infection, leading to acute infective bronchitis or, in more severe cases, the development of atelectasis and consolidation (pneumonia). These factors may contribute to poor gaseous exchange, decrease in ventilation perfusion, and breathlessness due to airflow limitation. If they