Peroxisome Proliferator-activated Receptor Gamma as Modulator of Inflammation in Pulmonary Sarcoidosis

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SUMMARY
Peroxisome proliferator-activated receptor (PPAR) includes the family of ligand-activated transcription factors which belong to the group of nuclear hormone receptors and are connected to retinoid, glucocorticoid and thyroid hormone receptors. There are three subtypes of PPARs: PPARα (also known as NR1C3), PPARγ (known as NR1C1) and PPARδ (known as PPARβ or NR1C2). All of them take part in the metabolism, cell proliferation and immune response. PPARγ and PPARα are identified as important immunomodulators and potentially represent an anti-inflammatory target for respiratory diseases. PPARγ deficiency in the lungs has been observed in the inflammatory diseases such as asthma, pulmonary alveolar proteinosis, fibrosis and sarcoidosis, as well as in the animal models of the lung inflammation. A small number of papers concerned with PPARγ in sarcoidosis point to the lowered activity of this factor in the alveolar macrophages and a lowered gene expression for the PPARγ, while the activity is preserved in healthy individuals. At the same time, an increased activity of the nuclear factor kappa B (NF-kB) in the bronchoalveolar lavage has been recorded in patients with sarcoidosis. The reason for the decrease in the production of PPARγ in sarcoidosis remains unknown. Several possible mechanisms are mentioned: genetic defect with lowered production, down-regulation due to the increased values of IFN-γ or an increased decomposition of PPARγ. Further investigation will explain the mechanisms regarding the decreased production of PPARγ in sarcoidosis.
Keywords: pulmonary sarcoidosis; bronchoalveolar lavage; peroxisome proliferator-activated receptor (PPAR)

INTRODUCTION

The mechanisms of the evolution and resolution of inflammation have been a burning research issue in the last two decades. Although lungs are incessantly exposed to the particles from the environment, allergens, microorganisms etc., they are not constantly infected or inflamed. The reason for this is the fact that alveolar macrophages and macrophages in the airways express numerous anti-inflammatory molecules which prevent development of the pulmonary inflammation. Alveolar macrophages play a double role: on one hand, they eliminate pathogens very fast; on the other, they have a major role in the onset of inflammation and immune response [1]. The first event in lung inflammation is the accumulation of neutrophils and other inflammatory cells from the circulation, which leads to development of pneumonitis. The joint action of all inflammatory cells and complement system initiates the process of opsonization and phagocytosis, which results in the elimination of pathogens. In the following days, monocytes accumulate in the alveolar space and differentiate into macrophages, i.e. alveolar macrophages. In this phase, the role of alveolar macrophages is to clean tissue, neutralize bacteria, and take part in the phagocytosis of neutrophils which undergo programmed cell death. This is the „service" that helps elimination of neutrophils from the airways and prevents the possible later damage of the alveolar epithelium. The activated alveolar macrophages begin the active production of the transforming growth factor β, anti-inflammatory cytokine which down-regulates the production of proinflammatory cytokines and has a vital role in the regulation of reparation of the connective tissue matrix. Current studies point out that all the aforementioned mechanisms participate in the suppression of pulmonary inflammation in the healthy lungs, as well as in the resolution of pulmonary inflammation [2].

Within the body, the process of an adequate ending of inflammation is equally important as its onset. However useful at the moment of pathogen elimination, the maintenance of inflammation has a myriad of side-effects on the tissue, including the destruction, irreversible damage and development of fibrosis. This is why an elaboration of the control mechanisms of inflammation in the body is essential for the maintaining of its regular function [1, 2].

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PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR (PPAR) γ AND INFLAMMATION

Peroxisome proliferator-activated receptors (PPAR) includes the family of ligand-activated transcription factors which belong to the group of nuclear hormone receptors and are related to retinoid, glucocorticoid and thyroid hormones [3]

There are three subtypes of PPARs: PPARα (also known as NR1C3), PPARγ (known as NR1C1) and PPARδ (known as PPAR β or NR1C2). All of them take part in the metabolism, cell proliferation and immune response [4]. Despite the fact that it was initially discovered to be important for the sugar and lipid metabolism, the role of this molecule in the regulation of inflammation, fibrosis and carcinogenesis has been increasingly studied in recent times [5]. PPARα is expressed in tissues which have a large degree of levels of carbolic-phenol fat acids, such as the liver, heart, kidneys and intestinal mucosa. PPARα is found in the pulmonary tissue, bronchial epithelium, T and B lymphocytes, alveolar macrophages and endothelial cells [2].

PPARγ is ligand-activated nuclear receptor which regulates the lipid and glucose metabolisms and participates in the negative regulation of inflammation. PPARγ is expressed on the pulmonary epithelium, submucosa, fibroblast, macrophages, eosinophils, T cells, B cells, dendritic cells and airway smooth muscles [6]. It has been proven that PPARγ has an essential role in the postnatal pulmonary development and the response to damage on animal models [7].

PPARγ and PPARα have been identified as important immunomodulators and are potential therapeutic target for airway diseases. The effects of PPARγ and PPARα are achieved mainly via their ability to affect gene expression for proinflammatory cytokines, which helps to reduce the inflammation processes. PPARγ deficiency in the lungs has been observed in the inflammatory diseases such as asthma, pulmonary alveolar proteinosis, fibrosis and sarcoidosis, as well as on animal models of pulmonary inflammation[8]. It has been proven that rat macrophages in the process of infection or inflammation produce an inducible nitric oxide synthetase (iNOS) [9]. Given the fact that high PPARγ gene expression has been proven for healthy individuals, it can be presupposed that deletion or lowered expression of this gene of the alveolar macrophages in vivo can result in the up-regulation of iNOS and other inflammatory mediators. The deletion of PPARs in the rat alveolar macrophages disturbs the pulmonary homeostasis on several levels [10]:

- iNOS and IFN are up-regulated in the alveolar macrophages
- the infiltration of T lymphocytes in the lungs is increased
- the production of cytokines by T helper 1 (Th1) response cells is increased, as well as the concentration of these cytokines in the bronchoalveolar lavage (BAL).

PPARs interact with a broad range of structurally distinct natural and synthetic ligands. Saturated and unsaturated fatty acids and eicosanoid derivatives have been identified as natural ligands of the PPARs activating them in micromolar concentrations. Thiazolidinedione, antidiabetic agents were first synthetic PPARγ agonists, and fibrates, well established in the therapy of dyslipidemia and hypertriglyceridemia, appear to exert their effect as PPARα ligands [3]. PPAR ligands inhibit the release of the proinflammatory cytokines from the activated alveolar macrophages, airways epithelial cells and eosinophils and play an important role in the regulation of the cell differentiation [2]. It was proven that PPARγ agonists function as the regulators of the epithelial cell inflammation by reducing the production of mucin induced by cigarette smoke in the cells of the respiratory epithelium [11]. The down-regulation of PPARγ in the cells of the broncho-alveolar lavage is a potential factor involved in the dysregulation of pulmonary homeostasis, suggesting the possible role of the PPAR agonists in treatment of the inflammatory respiratory diseases such as asthma, chronic obstructive pulmonary disease, sarcoidosis etc. The importance of PPARγ stimulation in the fibrosis process has been proven. The stimulation of PPARγ by synthetic or natural agonists considerably reduces pulmonary fibrosis caused by bleomycin in rats [12]. Furthermore, the fibroblasts of the patients suffering from various forms of pulmonary fibrosis show lowered fibrotic activity after the PPARγ stimulation [13]. Moreover, an administration of PPARγ agonists after the application of bleomycin fully prevents the development of fibrosis in rats, which points to the fact that PPARγ can have a direct antifibrotic effect independent of its anti-inflammatory mechanism [13]. Numerous studies highlight the important role of PPARγ in the regulation of cell growth, differentiation and apoptosis. The use of PPARγ agonists considerably increases the apoptosis of macrophages in the experimental research [14].

The opinion that PPARs could have immunomodulating properties and a potent inflammatory activity has raised the interest for this receptor. Studies have been conducted concerning its importance for a variety of diseases: diabetes type 2, atherosclerosis, inflammatory bowel disease, arthritis, myocarditis, cancer and endotoxic shock. In the models of inflammatory diseases where Th1 and Th17 responses are dominant, such as bowel diseases and arthritis, it has been proven that PPARγ can improve the clinical features of the disease by down-regulating the inflammatory cytokines [15]. Since sarcoidosis is also a disease with both Th1 and Th17 cell response [16], there is a hypothesis that PPARγ deficiency leads to the maintenance of inflammation in pulmonary sarcoidosis, increased production of the proinflammatory transcription factors, especially AP-1 and NF- kB[3]. PPARγ agonists are used in treatment of dyslipidemia and insulin-independent diabetes mellitus. Due to the important role of this molecule in the pathogenesis of various inflammatory diseases, the research is currently being conducted in order to test possible application of PPARγ agonists in the inflammatory bowel disease, rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, etc. [17, 18].

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PULMONARY SARCOIDOSIS AND PPARγ

Sarcoidosis is a multisystemic disease of the unknown etiology, characterized by the non-caseous granulomatous inflammation. The disease may start acutely, by Löfgren syndrome [19]. All the organs can be affected by sarcoidosis, most typically the lungs and the intrathoracic lymph glands. Certain sarcoidosis localizations are considered rare, such as breast sarcoidosis [20], central nervous system sarcoidosis or uterus sarcoidosis and can present a true diagnostic challenge. The diagnosis of sarcoidosis should include the combination of the clinical-radiological tests and the histological confirmation of the non-caseous epithelioid granuloma and the elimination of other granulomatous diseases with known genesis. The sarcoid granulomas are basic pathogen substrate in sarcoidosis, occurring due to the accumulation of macrophages and $CD4^+$ lymphocytes on the location of the disease. In the broncho-alveolar lavage, the cellular contents are considerably altered in such a way that there is an increased number of $CD4^+$ lymphocytes [21]. The initial trigger of the appearance of granuloma is an unknown antigen which is distributed to the alveoli aerogenously or hematogenously. This antigen persists in the tissue long enough to initiate an immunologic reaction of the cell type with the formation of granuloma. The key role in the formation of granuloma belongs to the alveolar macrophages which recognize the antigen, process it and present to other cells in the immune system. The macrophages of patients suffering from the sarcoidosis express a bigger amount of major histocompatibility complex (MHC) II molecule, intracellular adhesive molecule 1 (ICAM -1) and costimulatory molecules necessary to initiate the immune response when compared to healthy individuals. In addition, they initiate the inflammatory response by the production of various cytokines (TNF α, IL-1, IL-6, IFN-1, IL-15). All the aforementioned events result in the accumulation of the inflammation cells, especially $CD4^+$ and $CD8^+$ T lymphocytes, natural killer (NK) cells and neutrophils. In addition, an increased synthesis of the oxygen and nitric oxide radicals has been recorded in the granulomas, as well as the matrix metalloproteinase [22, 23].

In the last twenty years, a considerable attention has been paid to the analysis of cells and mediators of the bronchoalveolar lavage in patients with the pulmonary sarcoidosis and other interstitial diseases [24, 25]. The analysis of the cellular contents of BAL was introduced in late 1970s and is considered to be a liquid biopsy of the lungs. The analysed cells in the lavage originate from the disease location and their activity correlates with the activity of the disease. In healthy individuals, alveolar macrophages dominate in the differential relationship of the BAL cells in more than 90%; polymorphonuclears account for about 1.2%, while lymphocytes are represented with approximately 7% or 8%. In patients with pulmonary sarcoidosis, the lymphocytic alveolitis is recorded in BAL with the domination of $CD4^+$ T lymphocytes. BAL analysis is extremely important for the diagnostic cascade of the pulmonary sarcoidosis, as well as the interstitial changes in other conditions such as exogenic allergic alveolitis, pulmonary fibrosis and interstitial changes within the connective tissue disease [21, 25].

If granulomas were the consequence of the inflammatory response of the host to a specific antigen, the elimination of the antigen would result in an improved condition. However, a number of patients have the chronic form of sarcoidosis, with the development of the progressive pulmonary fibrosis. The reasons for such a turn in the disease are unknown. One of the possible mechanisms is that the maintenance of inflammation leads to the activation of fibroblasts, increased production of collagen and development of fibrosis [26].

The production of all these cytokines and proinflammatory molecules is normally suppressed by the activity of PPARγ; consequently, it is supposed that lowered activity of this molecule is one of the possible reasons for the occurrence of sarcoidosis [27].

A small number of research papers that explore the role of PPARγ in sarcoidosis point to the lowered activity of this factor in the alveolar macrophages, lowered expression of the PPARγ gene [8]; in contrast, this activity is preserved in healthy individuals, suggesting the down-regulation of this molecule during the pulmonary inflammation [28] At the same time, an increased activity of the NF-kB in BAL has been noted in patients suffering from the sarcoidosis. NF-kB is essential in the activation of the production of proinflammatory cytokines, whose increase has been recorded in patients with sarcoidosis[29]. Similarly, this molecule plays an important role in the regulation and control of inflammation and apoptosis [30, 31].

Since it is known that PPARγ is a negative regulator of the NF-kB activity, its imbalance could be the cause of development of disease. One of the mechanisms of granuloma maintenance in sarcoidosis may be decreased apoptosis in the granuloma cells [32]. Since the decreased activity of PPARγ was proven in BAL in patients with the chronic sarcoidosis, this might be the reason for the maintenance of Th1 and Th17 response and an increased production of the proinflammatory cytokines [17]. It is a fact that PPARγ down-regulates the synthesis of IL-1, tumor necrosis factor α (TNFα), and interferon γ (IFNγ). All these factors play an important role in the chronic sarcoidosis. On the other hand, PPARγ initiates the synthesis of GATA3, the transcription factor that in turn initiates the Th2 response [33]. A disturbed balance between Th1 and Th2 responses is certainly important for the development of sarcoidosis [29].

Given the fact that a group of patients developed the chronic form of the disease, with the pulmonary fibrosis, it is possible that there is an effect of a lower PPARγ activity in this process. Transforming growth factor β (TGFβ) induces fibroblast and myofibroblast proliferation *in vitro* and is one of the key activators of fibrosis [34]. An excessive expression of TGFβ in the lungs of a rat is coupled with the development of heavy, irreversible fibrosis, while its inhibition reduces the development of the pulmonary fibrosis [35, 36]. PPARγ ligands are strong inhibitors of

fibroblast and myofibroblast proliferation induced by TGFβ. In the rat models of scleroderma and fibrosis, the expression of PPARγ was considerably reduced. The application of PPARγ agonists can reduce or prevent the development of liver, pulmonary and kidney fibrosis on the experimental models. This could highlight the importance of this molecule in the development of chronic, progressive forms of the disease. The reason for the decreased production of PPARγ in sarcoidosis is not known. There are a few possible mechanisms mentioned: genetic defect with lowered production, down-regulation due to increased levels of IFN γ or increased decomposition of PPARγ [28, 37].

CONCLUSION

Additional experiments will explain the mechanisms concerning the decreased production of PPARγ in sarcoidosis. The existing studies exploring the importance of PPARγ in inflammation have been performed mainly on experimental models. The importance of this mediator in chronic diseases, including sarcoidosis, has been verified mostly on a small number of subjects and requires further research. To sum up, detailed research will certainly contribute to better understanding of the pathogenesis of the disease, as well as help to explore new therapeutic options concerning the application of PPARγ agonists.

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Гама рецептор активиран пролифератором пероксизома као модулатор запаљења у саркоидози плућа

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КРАТАК САДРЖАЈ

Рецептори активирани пролифератором пероксизома (*PPAR*) обухватају фамилију транскрипционих фактора активираних лигандима, који припадају породици рецептора за хормоне у једру и који су у вези с ретиноидом, глукокортикоидом и рецептором тиреоидног хормона. Постоје три подтипа *PPAR*: *PPARα* (познат и као *NR1C3*), *PPARγ* (познат као *NR1C1*) и *PPARδ* (познат и као *PPARβ* или *NR1C2*). Сви они учествују у метаболизму, пролиферацији ћелија и имунском одговору. *PPARγ* и *PPARα* су означени као важни имуномодулатори и потенцијално су терапијска мета код болести дисајних путева. Смањена активност *PPARγ* у плућима запажена је у инфламаторним болестима као што су астма, алвеоларна плућна протеиноза, фиброзе и саркоидоза, као и у анималним моделима запаљења плућа. Мали број радова који се односи на испитивање *PPARγ* у саркоидози указује на смањену активност овог фактора у алвеоларним макрофагима, смањену експресију гена за *PPARγ*, док је та активност очувана код здравих особа. У исто време уочена је и повећана активност нуклеарног фактора капа *B* (*NF-kB*) у бронхоалвеоларном лавату особа оболелих од саркоидозе. Разлог смањене производње *PPARγ* у саркоидози није познат. Помиње се неколико могућих механизама: генско оштећење са смањеном производњом, нисходна регулација због повишених вредности *IFN-γ* или повећана разградња *PPARγ*. Додатна испитивања објаснић механизме смањеног стварања *PPARγ* у саркоидози.

Кључне речи: саркоидоза плућа; бронхоалвеоларна лаважа; рецептор активиран пролифератором пероксизома (*PPAR*)

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