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Abstract	Ageing is generally defined as the progressive decline of homeostasis that occurs after the reproductive phase of life is complete and the "*soma becomes disposable*" and death is inevitable according to one theory of ageing. The complexity of the ageing process becomes strikingly evident in the lung where tissue maintenance and repair suffer from damage at the genetic level as well as tissue level. Moreover, lung function declines steadily in adulthood and if data for older adults are extrapolated, the outcome suggests an upper age limit beyond which life becomes impossible. In this review we cover the main changes to lung structure and function with age and the impact on respiratory health. We also describe the role that an aged immune system may play in the age-related decline in lung function and the major involvement of altered signalling through developmental pathways with special focus on PPARγ.	
Keywords (separated by " - ")	Lung function - Inflammation - PPARγ - Wnt - Ageing	

Immunosenescence and the Ageing Lung

6

Krisztian Kvell and Judit E. Pongracz

Abstract

Ageing is generally defined as the progressive decline of homeostasis that occurs after the reproductive phase of life is complete and the "*soma becomes disposable*" and death is inevitable according to one theory of ageing. The complexity of the ageing process becomes strikingly evident in the lung where tissue maintenance and repair suffer from damage at the genetic level as well as tissue level. Moreover, lung function declines steadily in adulthood and if data for older adults are extrapolated, the outcome suggests an upper age limit beyond which life becomes impossible. In this review we cover the main changes to lung structure and function with age and the impact on respiratory health. We also describe the role that an aged immune system may play in the age-related decline in lung function and the major involvement of altered signalling through developmental pathways with special focus on PPARγ.

Keywords

Lung function • Inflammation • PPARγ • Wnt • Ageing

6.1 Introduction

In a recent article [1] the association of age with lung function decline was summarized and showed a linear decline from maturity. If trajectories depicted in the paper are extrapolated (Fig. 6.1), it becomes evident that the absolute extent of human life is limited, at least in part, by respiratory function to about 130 years but currently there are no confirmed cases available of people who lived to the absolute limit of pulmonary functional decline. A rare exception is Mrs Tuti Yusupova of Uzbekistan who died in 2014 apparently at the age of 134 [2]. Although caution is

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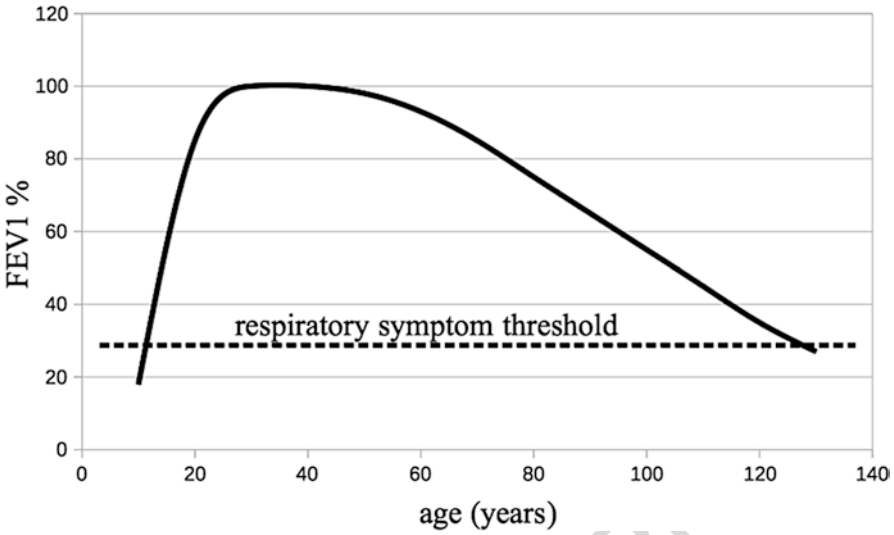

Fig. 6.1 Correlation of lung capacity with age (*dotted line* shows predicted respiratory symptom threshold), using data from [1]

required as her age has not been authenticated, she died as a very old person approaching the absolute limits of human life. The fully authenticated age to which any human has ever lived is 122 years and 164 days by Jeanne Louise Calment of France [3], who was born in 1875 and died in 1997. Ms Calment's and Ms Yusupova's very old age suggests that they suffered no detrimental co-morbidities and their genetic make-up regulating lung development, function and immune regulation was an enviably perfect combination. To understand more representative human ageing we have to use data from large population studies that have measured many aspects of human physiology, including lung function, over the lifespan.

6.2 Structural Changes of the Lungs During Pulmonary Senescence

The aged lung is characterised by airspace enlargement similar to, but not identical with acquired emphysema [4]. Such tissue damage is detected even in non-smokers above 50 years of age as the septa of the lung alveoli are destroyed and the enlarged alveolar structures result in a decreased surface for gas exchange [5] (Fig. 6.2). Tobacco smoking, pollution and hereditary factors are all involved in the regulation of emphysema making it difficult to separate the effect of accumulating environmental factors from the process of physiological ageing. Nevertheless, as total tissue mass and the number of capillaries decrease and formation of new alveoli becomes limited breathing difficulty is inevitable. Additional problems are that surfactant production decreases with age [6] increasing the effort needed to expand the lungs

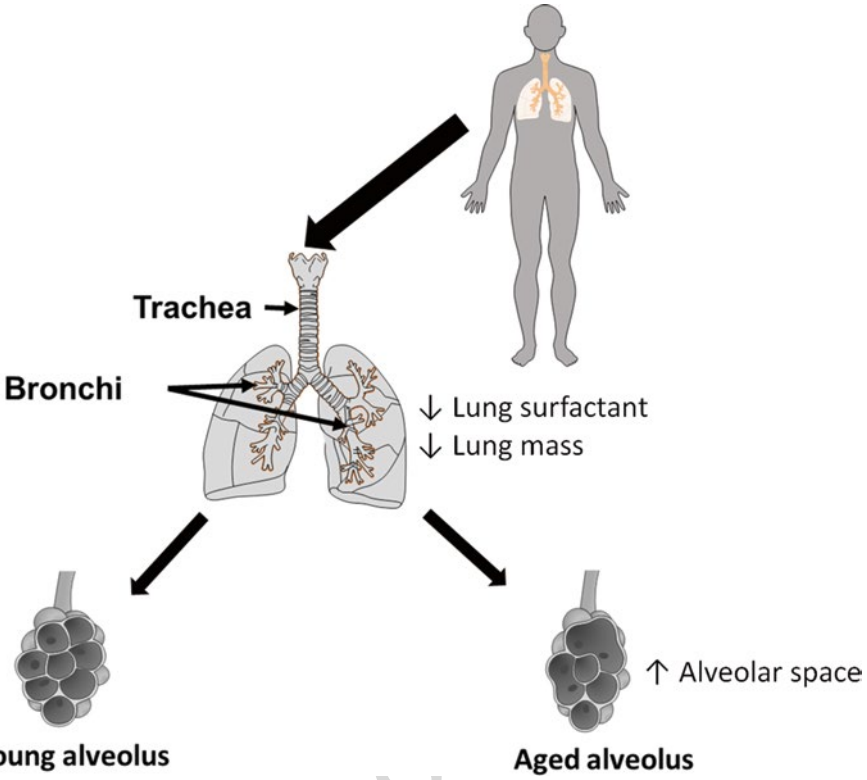

Fig. 6.2 Age-related changes of in the lung alveoli. The aged lung is characterised by airspace enlargement as the septa of the lung alveoli are destroyed and the enlarged alveolar structures result in a decreased surface for gas exchange. Total lung tissue mass and the number of capillaries decrease with age and formation of new alveoli becomes limited. Additionally surfactant production decreases with age increasing the effort needed to expand the lungs during inhalation

during inhalation in the already reduced thoracic cavity volume where the weakened muscles are unable to thoroughly ventilate. It is therefore no wonder that the decline of lung capacity is detected with age even if no specific disease is diagnosed [7, 8].

As ageing is associated with respiratory muscle strength reduction, coughing becomes difficult making it progressively challenging to eliminate inhaled particles, pollens, microbes, etc. Additionally, ciliary beat frequency (CBF) slows down with age impairing the lungs' first line of defence: mucociliary clearance [9] as the cilia can no longer repel invading microorganisms and particles. Consequently e.g. bacteria can more easily colonise the airways leading to infections that are frequent in the pulmonary tract of the older adult. In contrast to CBF, mucus production increases with age. Having mucus present in the airways intuitively appears to be beneficial as at baseline the mucus layer is needed to trap and eliminate inhaled particles and to prevent desiccation of airway surfaces. Mucus consists of an assortment of mucins and these high molecular-weight glycoproteins provide viscoelastic, gel-forming and

some anti-microbial properties to mucus. Understandably, the precise mucin composition of the mucus is important and whether it changes with age would be of high interest. Currently, however, very little is known about this aspect of mucin secretion. Interestingly, some recent animal studies revealed that while the production of mucus increases with age the ability of bronchial and alveolar cells to effectively produce mucus upon stimuli declines in the older animal [10] making the lungs more vulnerable to environmental factors.

6.3 Genetic and Epigenetic Regulation of Pulmonary Function

To identify the genetic background to lung function decline with age, several thousands of people have participated in various gene association studies [11, 12] that aimed to find correlations amongst gene locations, and specific genetic predisposition to senile emphysema as well as a closely associated disease: COPD. The result of such studies finally identified a locus on chromosome 4q31 that was associated with the percent of expected FEV1/FVC (as forced expiratory volume in 1 s [FEV1] and forced vital capacity [FVC]) ratio [11]. The locus was located in an intergenic region upstream of hedgehog interacting protein (HHIP), a hedgehog pathway gene with a known role in development. Additionally, six new genetic loci were identified that appeared to be associated with pulmonary function. These were located on chromosomes 2, 4, 5, 6 and 15 near genes including Tensin1 (TSN1) (2q35), encoding an actin-filament binding protein, four additional genes including Glutathione S-Transferase, C-terminal Domain (GSTCD) (4q24), Human Serotonin Receptor (HTR4) (5q32–33) a serotonin pathway gene, immune function genes Advanced Glycosylation End Product-Specific Receptor (AGER) and Palmitoyl-Protein Thioesterase 2 (PPT2) (6p21), a G-protein coupled receptor GPR126 (6q24.1) as well as Thrombospondin type 1 domain containing 4 gene (THSD4) (15q33) in the thrombospondin gene family [11]. Currently, it is not entirely clear how the elderly will directly benefit from the results of genome wide association studies. Certainly, further work is needed to identify the precise relevance to ageing and potential targets that could prolong pulmonary function.

In addition to specific genes, pulmonary senescence is also regulated by heritable modifications in gene expression that is not coded in the DNA sequence itself, but is rather governed by post-translational modifications in histone proteins and DNA. These modifications include chromatin remodeling (histone acetylation, methylation, ubiquitination, phosphorylation, and sumoylation) and DNA methylation. One of the most investigated epigenetic modulators of the ageing process are class I histone deacetylases [13]. Apart from various other cellular functions, for example, histone deacetylase 2 (HDAC2) regulates glucocorticoid function in inhibiting inflammatory responses and protects against DNA damage and cellular senescence as well as premature ageing in response to oxidative stress. Unfortunately, in ageing COPD patients HDAC2 is post-translationally modified by cigarette smoke leading to its reduction via an ubiquitination-proteasome dependent degradation process rendering glucocorticoid containing anti-inflammatory drugs ineffective during their treatment

[14]. Recently, NAD^+-dependent deacetylases known as sirtuins (SIRT1–SIRT7) have also been widely investigated for their role in the regulation of the ageing process [15]. The best characterized is SIRT1 and although its function in prolonging lifespan is currently under debate, it has been shown that through deacetylation of many transcriptional factors, SIRT1 modulates key events in ageing [16] including the oxidative stress response, endothelial dysfunction, and inflammation [17, 18]. Whether sirtuins modulate lung function is currently under investigation.

Age-associated alterations in gene expression are also intensively investigated at the level of small "non-coding" micro-RNAs (miRNAs) that post-transcriptionally regulate gene expression. Several miRNAs have already been reported to regulate the expression of SIRT1 including miR-217 [19] in endothelial cells, a downstream target of p53 microRNA, miR34a [20, 21], as well as miR-199a and miR-132 that mediate the regulation of chemokine production [22] or HIF-1α function [23]. Recently, some miRNAs including miR-1, miR-122 and miR-375, miR-21, miR-206, miR-30a that regulate conserved pathways of ageing, including insulin/IGF signalling (IIS), DAF-12 signalling and mTOR signalling, have been linked to human age-related disorders such as heart-, muscle- and neurodegenerative diseases [24]. Whether they are also involved in pulmonary senescence is currently unknown. The constantly present low level inflammation characteristic of ageing is also regulated by microRNAs e.g. miR-146a and thus could contribute to lung functional decline, this microRNA is also an important regulator of toll-like receptor dependent signalling pathways and therefore epithelial cell dependent immune responses [25].

6.4 Inflammaging and Immune Responses in the Lung

Structural changes of the ageing lung are regulated by genetically coded and acquired qualities that are tightly interconnected with systemic immune dysfunction and chronic, low level systemic inflammation, termed inflammaging. Inflammaging is the basal activation of the innate immune system in the absence of an immunologic threat [26] and is marked by elevated levels of tissue and circulating pro-inflammatory cytokines including interleukin (IL)-1β, IL-6, and tumour necrosis factor-α (TNF-α). Inflammaging combined with blunted innate and adaptive immune responses (see Chaps. 1 and 2) affects the lungs ability to fight infections and also leads to tissue remodelling.

In the adult healthy lung several immune cell types are resident at various anatomical sites including bronchial, interstitial and alveolar macrophages, dendritic cells, interstitial T- and B-lymphocytes [27]. Their presence is highly important as our lungs are in constant and direct contact with the environment via epithelial surfaces. During ventilation the lung surfaces are exposed to various microbes, particles and potentially damaging physical forces. Together with a variety of pulmonary epithelial cell types, the resident macrophages, T-cells and dendritic cells orchestrate the active protection of the lung tissue. During ageing the same is expected of the above cell types; however, immune cells change with age and their response to stimuli is no longer the same as in a young, healthy adult (see Chaps. 1 and 2).

The immunological defence of the lungs employs both innate and adaptive immune responses against antigens. Innate immunity is the critical first line of defence for the lungs while adaptive (acquired) immunity is antigen-specific and is required to ward off encapsulated bacteria, viruses, and intracellular pathogens. This form of immunity relies on immunological memory and antibody production. However, important changes in immunological responses occur with age and the impact on lung immunity can be summarised as follows:

6.4.1 Lung T-Cells

In histologically normal (not inflamed) human lung parenchyma there are approximately 1×10^{10} CD3 positive T-cells in residence. These T-cells are mainly tissue resident memory cells enriched for the immune response to local environmental antigens. This suggests that tissue resident T cells are present to maintain peripheral immune defence and that recruitment of memory T cells from blood or lymph nodes may not be necessary to recall an immune response in the lung. Memory T-cells originate from a pool of progenitor cells developing in the thymus that are undergoing a complex differentiation, selection and maturation process then encounter their T cell receptor (TCR)-specific antigen to finally mature into memory cells. However, naïve T-cell output progressively decreases with age due to involution of the thymus [28]. Epithelial cells that turn into adipocytes with age in the thymus, can no longer support T-cell differentiation and selection [28]. Consequently, the T-cell pool in the lung parenchyma can no longer be replenished by freshly released naïve T-cells reducing fast and effective immune reactions against novel antigens. Although lung-specific analysis of T-cell subtypes awaits further studies, data indicate that intrinsic deficiencies and defects in signalling, such as pathways involving T-cell cytokine production that lead to Th2 differentiation, are seen in old T cells [29].

6.4.2 Dendritic Cells (DCs)

Professional, antigen presenting DCs play a critical role in linking innate and adaptive immunity. Lung DCs are categorized as conventional DCs (cDCs), plasmacytoid DCs (pDCs) and monocyte-derived DCs (moDCs) each representing independent developmental lineages. Lung DCs develop in the bone marrow and enter the lung as pre-DCs that are thought to differentiate locally into mature DC subsets [30]. Although changes in pattern recognition and toll-like receptor expressions have not yet been reported during ageing in lung DCs, antigen uptake by pinocytosis has been shown to be less effective and cytokine expression profiles alter so that instead of Th1, they promote Th2-type T-cell responses [31]. Such a skewed response may help responses to extracellular infections but may dampen Th1 inflammatory responses to intracellular pathogens such as respiratory viruses.

6.4.3 Macrophages

Tissue macrophage subsets, including lung alveolar macrophages (AMs), often arise from embryonic progenitors that seed the organs and mature locally before and shortly after birth [31]. GM-CSF instructs lung foetal monocyte differentiation shortly before and after birth through activation of the nuclear receptor PPARγ [32]. Deletion of PPARγ in AMs of experimental animals resulted in pulmonary alveolar proteinosis (PAP) a process seen in patients with PAP who have low expression of PPARγ in AMs. AMs are maintained by proliferative self-renewal throughout life autonomously, independent from bone marrow–derived monocytes. It has been established that AMs suppress immune responses through the inhibition of DC-mediated activation of T cells and production of transforming growth factor β (TGFβ). Recent studies have also shown that TGFβ-induced Foxp3+ Treg cells (iTreg cells) inhibit spontaneous and antigen-induced development of Th2-type airway inflammation and induce tolerance to inhaled innocuous antigens [33]. The process is AM- and not DC-dependent and occurs in the lung tissue, not in the draining lymph nodes. In AMs, the switch from a tolerogenic mode to an inflammatory mode is accompanied by the secretion of IL-1, IL-6, TNFα and a latent TGFβ secretion where the latter only becomes activated by the integrin αVβ6 expressed on alveolar epithelial cells (AECs). In the absence of αVβ6 on epithelial cells spontaneous inflammation and emphysema develop [34]. Data indicate that detachment of AMs from epithelia upon infection may unleash AM inflammation by withdrawal of active TGFβ. Inhibition of pathological airway inflammation occurs via the intercommunication of AMs located in alveoli through the alveolar epithelium communication. The prevention of inflammatory responses is mediated by various inhibitory receptors on AMs, with the ligands expressed on AECs or present in the alveolar fluid [35].

With respect to ageing, recent studies resulted in controversial data when investigating senescent macrophages. In mouse studies some differences in TLR expression and cytokine responses as well as differentiation from macrophage progenitors were detected, but these have not all been observed or even investigated in human ageing studies. Nevertheless, aged macrophages exhibit low-grade pro-inflammatory phenotype and significantly reduced levels of autophagy that contribute to accelerated changes in the ageing process in general [36]. Unfortunately, little is known about specific changes characteristic to human alveolar or bronchial resident macrophages with age.

6.4.4 Lung Neutrophils

Neutrophils play a pivotal role in lung inflammation, but also clearance during and following inflammation. The role of neutrophils has been shown in a number of inflammatory lung diseases including ARDS, COPD, cystic fibroses, idiopathic pulmonary fibrosis, bronchiectasis and asthma [37]. It appears that following a successful inflammatory response neutrophils can change from a pro-inflammatory to an anti-inflammatory phenotype. In this case, neutrophils stop producing and releasing pro-inflammatory mediators (i.e. leukotriene B4, platelet-activating factor, IL-8) and instead begin to release resolving mediators including bioactive lipids (i.e. lipoxins, resolvins) that enhance resolution following inflammation [38].

With age there are dramatic changes in neutrophil function, including reduced chemotaxis, phagocytosis and bactericidal mechanisms (fully reviewed in Chap. 1). The reduced bactericidal function will predispose to infection but the reduced chemotaxis also has consequences for lung tissue as this results in increased tissue bystander damage from neutrophil elastases released during migration [39]. This reduced chemotactic behavior is due to dysregulated PI3 kinase intracellular signaling rather than reduced surface expression of chemoattractant receptors [40]. Neutrophil granulocytes are acknowledged as key players of COPD, increased neutrophil lung populations are associated with tissue damage, increased inflammation and impaired tissue repair. There is recent evidence suggesting that neutrophil functions (migration, ROS generation, degranulation, phagocytosis) are also all impaired in COPD resulting in bias towards increased inflammation and reduced bacterial clearance [40].

6.4.5 Epithelial Cells

The numerous roles of various pulmonary epithelial cells include mucin production, mucociliary clearance in conducting airways, reduction of surface tension in the alveoli of pulmonary host defences are well integrated with the ability of respiratory epithelial cells to respond to and 'instruct' the professional immune system to protect the lungs from infection and injury. For example surfactants lower surface tension and are also involved in immune function. While the type II alveolar epithelial differentiation marker is surfactant protein C, the immune function of surfactants is primarily attributed to two surfactant proteins: A and D. They can both opsonize pathogens for phagocytosis. Low surfactant production, degradation or inactivation may therefore contribute to enhanced susceptibility to lung inflammation and infection. Furthermore, interaction of the signal-regulatory protein SIRPα (which mediates a so-called 'do not eat me' signal) on AMs with the globular heads of the surfactant proteins surfactant protein-A and surfactant protein-D suppresses AM inflammatory responses and phagocytosis, which can be overcome by TLR4 triggering that down-regulates SIRPα [41].

During ageing the pulmonary epithelium changes: the level of PPARγ decreases in both the alveolar epithelium and the supporting fibroblasts, consequently AECs become less capable of secreting surfactants which results in inefficient antimicrobial function and increased inflammatory cytokine production. Although it has not been reported in the context of pulmonary ageing, one can speculate that the process might be the same in several tissues where pro-fibrotic mediators are upregulated. There is evidence that the TGF-β/Smad3 pathway forms with αvβ6 integrin, mTOR and PPARγ a complex signalling network with extensive crosstalk regulating the development of fibrosis. In a rodent study it has been demonstrated that during colorectal fibrosis up-regulation of TGFβ, Smad3, αvβ6 and mTOR expression was detected while PPARγ expression was reduced [42].

6.5 PPARγ: A Prominent Member of the PPAR Family in the Ageing Lung

PPARγ expression and function appear to have a pivotal role in all molecular and cellular events associated with pulmonary senescence. PPARα, PPARβ, and PPARγ all show a common structure consisting of 4 domains: a variable amino terminal activation function-1 domain (AF-1), a DNA binding domain, a hinge region, and a conserved activation function-2 domain (AF-2). Domain AF-2 enables PPARs to bind structurally diverse natural and synthetic ligands [43]. In addition, AF-2 associates with co-regulators affecting receptor activity, receptor dimerization and nuclear translocation [44]. PPARs function as hetero-dimers with retinoid X receptors (RXR). Hetero-dimerization of PPAR with RXR is influenced by competing PPAR isoforms and other nuclear receptors. In their absence PPAR-RXR associates with co-repressor proteins of histone deacetylase activity. Ligands trigger co-repressor dissociation, and recruitment of co-activators [45]. Transcriptional activation or suppression may happen after recognition of PPAR response elements (PPRE) in target gene promoters and binding to PPRE consensus sequences [46].

PPARγ is a prominent member of the PPAR family and was first described as a regulator of adipocyte differentiation. Activation of PPARγ is triggered by a wide variety of natural as well as synthetic ligands. Natural PPARγ ligands include polyunsaturated fatty acids (PUFAs), eicosapentaenoic acids, and oxidized lipids [47]. The most studied family of synthetic ligands are the thiazolidinediones (TZDs). TZDs are used in the treatment of type 2 diabetes as they show insulin-sensitizing and hypoglycemic effects via activation of PPARγ [48]. Activation of PPARγ by TZDs results in the transcription of numerous genes involved in glucose and lipid utilization [49]. Examples for synthetic ligands include rosiglitazone (RGZ), ciglitazone (CGZ), pioglitazone (PGZ), and troglitazone (TGZ) [50].

6.5.1 PPAR Expression in Immune Cells and the Lung

PPARs are expressed in various cells of the immune system and the lungs (Table 6.1). PPARα and PPARγ are both expressed in macrophages and monocytes [51], eosinophils [52], with PPARβ also being expressed in neutrophils [37]. Dendritic cells only express PPARγ [53], while both PPARα and PPARγ are expressed by lymphocytes [54, 55]. PPARβ and PPARγ are both expressed in mast cells [56], while all three isoforms are present in airway epithelial cells [57]. As for mesenchymal cells, PPARγ is expressed by fibroblasts [58], while PPARα and PPARγ are present in airway smooth muscle cells [59]. These distinct patterns of expression suggest that activation of different isoforms may specifically regulate the production of inflammatory mediators and cellular responses.

There is increasing evidence suggesting that PPAR receptor patterns change in various lung disease, with PPARγ being the most extensively studied. Literature consensus for the role of PPARγ expression in the lungs is that it is up-regulated in response to diverse inflammatory conditions providing a negative feedback loop

t1.1 **Table 6.1** PPARγ-
t1.2 expressing immune and
t1.3 pulmonary cells

Cell type/subtype	PPARγ
Immune cells	
Lymphocytes	+
Monocyte/MØ	+
Neutrophils	+
Eosinophils	+
Dendritic cells	+
Pulmonary cells	
Epithelium	+
Fibroblasts	+
Smooth muscle	+

that allows natural PPARγ ligands to limit inflammatory responses in the lungs [60]. There is mounting evidence that PPAR ligands affect inflammatory processes through influencing cellular immune responses. These actions overlap with corticosteroids, exerting inhibitory effects on T cells, eosinophils, neutrophils, mast cells/basophils, and macrophages [61], with studies mostly focusing on PPARγ [62].

The PPARγ ligands PGJ2 and CGZ were reported to inhibit T cell proliferation [63]. PGJ2 efficiently induces T cell apoptosis and can also decrease the production of both Th1 and Th2 type cytokines from T cells [64]. Moreover, T cells treated with CGZ show decreased IFNγ, IL-4, and IL-2 secretion [65]. On the other hand, PGJ2 may also potentially trigger inflammation through the induction of IL-8 expression in T cells and macrophages via MAPK and NfkB signalling [66]. In monocytes, PGJ2 and TGZ efficiently inhibit the secretion of tumour necrosis factor α (TNFα), interleukin-1β (IL- 1β) and IL-6 [67]. PGJ2 and RGZ also decrease TNFα release and the expression of inducible nitric oxide synthase (iNOS) and matrix metalloproteinase (MMP)-9 in macrophages through inhibiting the activities of AP-1, STAT, and NFkB. Moreover, both PPARα and PPARγ ligands promote macrophage apoptosis as well [66, 67].

6.5.2 The Role of PPARγ in Pulmonary Tissue Homeostasis and Ageing

Tissue-specific stem cells have already been identified for many tissues. In the lungs alveolar type II cells (ATII), are essential for the development and repair of the gas-exchange surface. Surfactant protein production and survival of ATII cells is supported by lipofibroblasts, and their differentiation is PPARγ-dependent [68]. The process is strongly influenced by the Wnt/β-catenin signaling pathway: in the case of PPARγ-dominance lipofibroblast differentiation is skewed towards myofibroblast differentiation that does not support ATII replenishment. With age PPARγ expression decreases, while Wnt secretion increases. Consequently, stem cell capacity to renew the ATII cell pool decreases and as does pulmonary regenerative capacity shrink with age that renders the lungs more vulnerable to various diseases and conditions [6]. However, reinforcing PPARγ activity through TZD administration

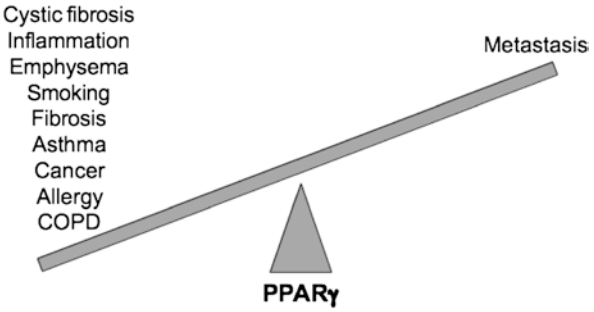

Fig. 6.3 Conditions related to diminished PPARγ activity (*left*) outweigh those linked with elevated PPARγ activity (*right*) in the lungs

has been shown to induce myofibroblast transdifferentiation into lipofibroblast cells. This may replenish the stem cell pool of pulmonary tissues, potentially counteracting the pro-ageing decrease of PPARγ activity observed during physiological senescence [69].

It is currently accepted that alterations in pulmonary PPAR profile, more precisely loss of PPARγ activity, can lead to inflammation, allergy, asthma, COPD, emphysema, fibrosis, and cancer (Fig. 6.3) [70]. Since it has been reported that PPARγ activity decreases with age, this provides a possible explanation for the increasing incidence of these lung diseases and conditions in older individuals [6]. The significance of maintaining PPARγ-activity in the lungs has led to research looking for potential novel biomarkers and therapeutic targets. A simplified approach would postulate TZDs as universal adjuvants for the treatment of various lung diseases and age-related pulmonary conditions. However, one must keep in mind that TZDs have a history in human therapy being used for the oral treatment of type 2 diabetes (PPARγ decreases insulin resistance) and certain TZDs have been restricted due to an increased incidence of cardiac events [71]. For pulmonary treatment this risk may be circumvented if nebulized TZDs are applied that maximize local efficiency and minimize systemic side effects [72]. Nevertheless, there are also reports on the potential harmful effects of TZDs with respect to lung cancer cell dissemination (not formation) by rendering the pulmonary micro-environment permissive for tumour cell survival [73].

6.6 The Role of PPARγ in Ageing Associated Pulmonary Diseases

Pulmonary tissue inflammation is often associated with ageing and may be triggered by various factors including infectious or chemical agents, but may also be initiated by endogenous factors as in the case of autoimmune conditions [74]. Despite the diversity of lung inflammation triggering factors the subsequently activated pro-inflammatory pathways are often shared. PPARγ can efficiently act on these pathways as it inhibits transcription factors regulating the expression of pro-inflammatory genes such as NF-kB, STAT-1 and AP1 [75, 76]. Activated PPARγ is capable of

sequestering co-activator complexes on the promoter regions of pro-inflammatory genes that renders them inaccessible to these transcription factors. Also, PPARγ activation leads to the production of suppressive mediators, such as TGFβ and IL-10 that might be even more significant in the local micro-environment niche [77, 78]. As a consequence PPARγ up-regulation potentiates inhibitory loops that provide the molecular basis for resolution following an initially inflammatory response.

6.6.1 COPD

Chronic obstructive pulmonary disease (COPD) is common in older people, with an estimated prevalence of 10 % in the US population aged ≥75 years. Inhaled medications are the cornerstone of treatment for COPD and are typically administered by one of three types of devices (pressurized metered dose inhalers, dry powder inhalers, and nebulizers). However, age-related pulmonary changes may negatively influence the delivery of inhaled medications to the small airways [79]. In addition, physical and cognitive impairment, which are common in older patients with COPD, pose special challenges to the use of handheld inhalers in the old. Nebulizers should be considered for patients unable to use handheld inhalers properly. Airway mucus hypersecretion (AMH) is a key pathophysiological characteristic of COPD. Corticosteroid is the first-line anti-inflammatory treatment used to alleviate COPD, but its therapeutic effects are controversial and long term treatment often leads to undesirable side effects [80]. According to recent reports PPARγ agonists can inhibit mucin synthesis both in vitro and in vivo, but only nebulized TGZs lead to a reduction in mucus production in the airways, whereas oral administration has no such effect [81]. Administration of the PPARγ agonist ciglitazone via nebulizer reduces OVA-triggered mucus gland hyperplasia and airway occlusion by approximately 75 % [82]. It has been proposed that PPARγ activation may ease AMH through a pathway involving MMP-9, providing molecular mechanism of action for COPD treatment [83].

6.6.2 Lung Fibrosis

Currently approx. five million people are affected by pulmonary fibrosis worldwide. In most cases, patients are 40–50 years old at diagnosis, while the incidence of idiopathic pulmonary fibrosis increases drastically ≥50 years of age [84]. Fibrosis or fibrotic remodelling of lung tissue is a severe outcome of various lung diseases. Inflammatory cell invasion, epithelial cell injury and failure of re-epithelialization are followed by recruitment and persistence of fibroblasts. Excessive collagen and extracellular matrix production results in lung fibrosis [85]. Reduced PPAR expression was shown in lung fibroblasts of patients with dysregulated inflammation and fibrosis [86]. Studies found that TZDs were able to inhibit lung fibrosis [86]. PPAR ligands have negative effects on human lung fibroblasts by inhibiting proliferation and migration triggered by mitogenic growth factors such as PDGF [87]. Furthermore, PPAR agonists inhibit lung fibroblast differentiation mediated by

TGFβ and significantly reduce the expression of fibronectin and type I collagen [88]. Anti-fibrotic effects of TZDs has been demonstrated in animal models even after strong pro-fibrotic exposure (i.e. bleomycin) confirming them as potential candidates for therapy [89].

6.6.3 Lung Cancer

Lung cancers (LCs) have been defined as a major disease of the aged with disappointing survival statistics and represent the second most common type of cancer in both genders worldwide [90]. Another major inducer of LCs is cigarette smoking, although specific LC subtypes do not correlate with either age or smoking status (i.e. lung adenocarcinoma is more characteristic of young females) [91]. Cigarette smoke has also been shown to decrease PPARγ expression in the lungs leading to detrimental effects suggesting that PPARγ agonist treatment may counteract negative effects related to smoking and ageing. Indeed it was shown that treatment targeting PPARγ can significantly inhibit cigarette smoke-induced mucin production [92]. It has also been reported that exposure to acrolein, one of the most toxic compounds found in cigarette smoke, induces goblet cell hyperplasia in bronchial epithelium and induces airway inflammation, as shown by the increased levels of inflammatory cytokines including IL-1β, IL-8, and TNF-α in bronchial fluid. Treatment with TGZs before acrolein exposure was reported to alleviate these changes in a dose-dependent manner providing evidence for PPARγ efficiency in counteracting smoking [75]. These studies suggest a role of PPARγ in lung tumorigenesis, and suggest PPARs as potential biomarkers of lung tumours. Furthermore, the enhancement of PPARγ activity (through i.e. TZDs) could prevent the formation of lung cancer, or serve as adjuvant during lung cancer therapy. However, once tumour cells have been formed the situation may change. It has been reported that systemic administration of TGZs accelerates tumour metastasis in models of non-small cell lung cancer [93] and does not provide any survival benefit. Therefore systemic administration of PPARγ agonists to be avoided in advanced lung cancer, but again local administration perhaps via inhalers may reach the desired effect.

6.7 The Role of Wnt Pathways in Pulmonary Senescence: Regulation of PPARγ

Although PPARγ seems to play an important role in the differentiation and function of a great variety of pulmonary cell types, the question remains: why would PPARγ level and activity alter with age? Pinpointing the initial molecular trigger is difficult but recent studies highlighted the imbalance in Wnt signalling as age progresses [94]. Importantly, the opposition between PPARγ and the Wnt / β-catenin pathway has already been reported in several tissues by multiple research groups including ourselves [95]. It is conceivable that the pulmonary (epithelial) setting is similar in showing reciprocal changes of PPARγ and Wnt expression or activity with age. Indeed, increased Wnt4 and Wnt5a secretion in the ageing lung has been observed

and both Wnts were reported to down-regulate PPARγ using a different mechanism [unpublished observations]. Reduction in PPARγ also leads to a decreased number of the alveolar progenitor or ATII cells; which can explain age-associated reduction in regenerative capacity. As ATII cells are also the source of surfactants, reduction in SP-levels indicates weakened functionality of ATII-s that was documented in both ageing animals as well as in the primary human lung tissue [96].

6.8 Conclusion

In summary, accumulated data suggest that although complexity of the ageing process is evident, by targeting some general molecular regulators (notably PPARγ signalling) using carefully designed, organ and tissue specific delivery methods, might allow us in the future to counteract the ageing program and delay decline of pulmonary function.

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