Pharmacology & Therapeutics 153 (2015) 125–134

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Associate editor: J. Burgess

Telomere Dysfunction and Cell Senescence in Chronic Lung Diseases: Therapeutic Potential

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ARTICLE INFO

Available online 18 June 2015

Keywords:
Cellular senescence
lung disease
COPD
emphysema
pulmonary hypertension

ABSTRACT

Cellular senescence – defined as a stable cell-cycle arrest combined with stereotyped phenotypic changes – might play a causal role in various lung diseases, including chronic obstructive pulmonary disease (COPD), which is predicted to become the third leading cause of death worldwide by 2020. COPD is characterized by slowly progressive airflow obstruction and emphysema due to destruction of the lung parenchyma and is often complicated by pulmonary hypertension (PH). No curative treatment is available. Senescent cells, which accumulate with age, are increased in lungs from patients with COPD and express a robust senescence-associated secretory phenotype (SASP), which is proinflammatory.

The aim of this review is to show how senescent cells can drive the lung alterations seen in COPD, which mechanisms may be involved, and whether therapeutic interventions may slow or delay the in vitro cell-senescence process and in vivo lung alterations.

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Contents

1. Introduction . . . 125
2. Cellular senescence in pathology . . . 126
3. Chronic obstructive pulmonary disease (COPD) as a paradigm for age-related lung diseases . . . 128
4. Cell senescence as a common denominator for lung and systemic alterations in COPD – Role for the SASP . . . 128
5. Potential for new therapies . . . 130
6. Targeting cell senescence in COPD . . . 130
7. Cell senescence and the risk of cancer in COPD . . . 132
8. COPD, the optimal disease for clinical trials targeting cell senescence . . . 132
9. Disclosures . . . 132
Acknowledgments . . . 132
References . . . 132

Abbreviations: SASP, senescence associated secretory phenotype; PA-SMCs, pulmonary artery smooth muscle cells; P-ECs, pulmonary vascular endothelial cells; AECs, alveolar epithelial cells; COPD, chronic obstructive pulmonary disease; PH, pulmonary hypertension; p16, tumor suppressor protein p16, cyclin-dependent kinase-4 inhibitor; Pap, mean pulmonary artery pressure; Sap, mean systemic arterial pressure; PVR, pulmonary vascular resistance; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; BMI, body mass index; PDL, population doubling level; β-gal, beta-galactosidase; α-SMA, alpha-smooth muscle actin; Rb, retinoblastoma; IL-6, interleukin-6; IL-8, interleukin-8; MCP-1, monocyte chemoattractant protein 1; mTOR, mammalian target of rapamycin; TNF-α, tumor necrosis factor-alpha; IL-1β, interleukin-1-beta; TGF-β, transforming growth factor-beta; PDGF, platelet-derived growth factor; FCS, fetal calf serum; HDAC, histone deacetylase; Akt, serine/threonine kinase; vWF, von Willebrand factor.

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1. Introduction

Mounting evidence indicates that cell senescence – defined as a stable cell-cycle arrest combined with stereotyped phenotypic changes – might play a causal role in various lung diseases (Armanios & Blackburn, 2012). Senescent cells accumulate with age; are found at sites of age-related disease, including those targeting the lung; and express a robust senescence-associated secretory phenotype (SASP), which is proinflammatory (Armanios, 2013). Recent work by our groups and others has shown that cellular senescence contributes to lung diseases whose frequency increases with age, including chronic obstructive pulmonary disease (COPD) and lung fibrosis (Tsuji, Aoshiba, & Nagai, 2006;

http://dx.doi.org/10.1016/j.pharmthera.2015.06.007
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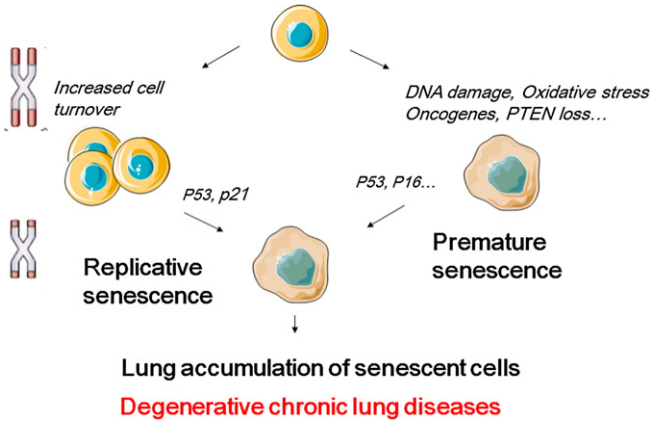

Fig. 1. Cellular senescence may be triggered by two different mechanisms. Replicative senescence is ascribed to progressive telomere shortening secondary to incomplete chromosomal replication in somatic cells, which divide but do not possess telomerase activity. Premature senescence may occur in response to various stress stimuli, such as oxidative stress, oncogenes, ionizing radiations, and PTEN loss. Telomeric signals and DNA damage principally engage the p53-p21 pathway, while nontelomeric signals engage either the p53-p21 or the p16-retinoblastoma protein pathway. The relative contributions of the p53-p21 and the p16-retinoblastoma protein pathway vary according to the stress stimulus, although both may ultimately become engaged at the stage of sustained cell senescence. The p16 tumor suppressor is now considered a robust biomarker of mammalian aging, a major effector of the cell senescence process, and an excellent indicator of the presence of senescent cells.

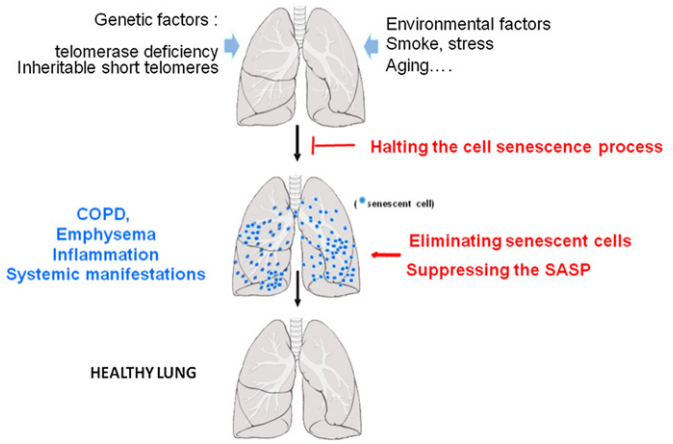

Fig. 2. Pathogenic mechanisms leading to COPD. Several arguments support the concept that telomere dysfunction and exaggerated lung cell senescence are major players in the pathogenesis of the lung alterations of COPD: (i) Subjects with COPD or emphysema exhibit short telomeres in lung and circulating cells; (ii) some individuals with telomerase gene mutations develop early lung emphysema instead of lung fibrosis, especially if they smoke; (iii) there is an accumulation of senescent alveolar-epithelial and endothelial cells and fibroblasts in lung specimens from patients with emphysema and COPD; (iv) pulmonary vascular endothelial and smooth muscle cells, as well as lung fibroblasts, from patients with COPD exhibit increased susceptibility to replicative senescence compared to controls; (v) mice with telomerase deficiency have an increased susceptibility to develop pulmonary emphysema after exposure to cigarette smoke; (vi) mediators and inflammatory cytokines released from senescent cells affect lung tissue remodeling and contribute to sustained inflammation in COPD; (vii) remodeling of pulmonary vessels at the origin of pulmonary hypertension (PH) in COPD is linked to the SASP of vascular senescent cells. Halting the cellular senescence process, eliminating senescent cells, and suppressing the SASP are three potential strategies for counteracting the deleterious effects of senescent cells in COPD.

Amsellem et al., 2011; Noureddine et al., 2011; Armanios, 2013; Dagouassat et al., 2013). This area of respiratory research has received considerable impetus from the finding that some cases of familial pulmonary fibrosis or pulmonary emphysema are associated with a mutation in the telomerase *TERT* gene and, therefore, are considered to be telomere disorders (Armanios et al., 2007; Armanios & Blackburn, 2012; Stanley et al., 2014). The hypothesis that cell senescence is a shared process in the pathogenesis and progression of age-related lung diseases is inspiring efforts to identify the mechanisms of cellular senescence in these diseases and to develop therapeutic strategies targeting these mechanisms. (See Figs. 1 and 2.)

Although sound evidence supports a detrimental role for cell senescence in both COPD and lung fibrosis, its effect in other conditions, such as pulmonary hypertension (PH), is more complex and possibly beneficial. PH is a proliferative disease of the pulmonary vascular cells and shares several features with cancer (Adnot, 2005). Inducing cell senescence might therefore be useful to limit the proliferative capacity of vascular cells in PH. However, PH may occur as a complication of COPD and lung fibrosis, a situation characterized by highly complex pathogenic mechanisms (Minai, Chaouat, & Adnot, 2010).

2. Cellular senescence in pathology

2.1. Cellular senescence

Cellular senescence is a stable growth arrest that occurs when cells experience potentially oncogenic insults (Campisi, 2005a,b). Senescent cells have a complex phenotype characterized by irreversible cell-cycle arrest mediated predominantly by p21 and/or p16, increased cell size, altered morphology, resistance to apoptosis, altered gene expression including up-regulation of β-gal, and a unique secretory phenotype known as the SASP (Coppe, Desprez, Krtolica, & Campisi, 2009).

Several processes have been identified that cause or are associated with cellular senescence. All of them increase with age. Briefly, senescence may be triggered by two different mechanisms. Replicative senescence is ascribed to progressive telomere shortening secondary to incomplete chromosomal replication in somatic cells, which divide but do not possess telomerase activity (Hayflick, 1965; Mathon & Lloyd, 2001). Premature senescence, in contrast, occurs in response to various stress stimuli, such as oxidative stress, oncogenes, and ionizing radiation (Mathon & Lloyd, 2001). Most of these stress stimuli, similarly to telomere erosion, activate the DNA damage response (DDR), a signaling pathway in which ATM (ataxia-telangiectasia mutated) or ATR (ataxia telangiectasia and Rad3-related protein) kinases block cell-cycle progression through activation of p53 and expression of the cyclin-dependent kinase inhibitor p21 (Cesare & Karlseder, 2012; van Deursen, 2014; Malaquin, Carrier-Leclerc, Dessureault, & Rodier, 2015). In contrast, nontelomeric signals, such as those induced by metabolic mechanisms (including PTEN loss), engage the p16/retinoblastoma protein pathway (Mathon & Lloyd, 2001; Campisi, 2005a,b; Armanios & Blackburn, 2012). At the stage of sustained senescence, however, or in pathologic conditions, both the p53-p21 and the p16/retinoblastoma pathways become engaged, and the two mechanisms of cell senescence are interconnected. In the lung, repeated insults such as cigarette smoke exposure, inflammation, or infections can induce not only premature senescence, but also replicative cell senescence due to the increased cell turnover and subsequent telomere shortening associated with lung-tissue repair (Tsuji, Aoshiba, & Nagai, 2004). Most of the lung cells seem involved in these processes, including the airway epithelial cells, alveolar epithelial cells, fibroblasts, vascular endothelial cells (ECs), and vascular smooth-muscle cells (SMCs) (Tsuji et al., 2006; Amsellem et al., 2011; Noureddine et al., 2011; Dagouassat et al., 2013). Thus, at the stage of in vivo cell senescence, and especially in complex diseases such as COPD, many molecular pathways seem implicated, further complicating the development of therapeutic strategies for targeting cell senescence.

2.2. Assessment of cellular senescence

2.2.1. Telomere shortening as a marker for lung-cell senescence

Telomere shortening in circulating leukocytes has been reported in various lung diseases, including familial and nonfamilial forms of lung fibrosis, COPD, and chronic asthma; as well as in PH complicating

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