REVIEW ARTICLE

Lung cancer in chronic obstructive pulmonary disease patients: importance of cellular senescence

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KEY WORDS

aging, cellular senescence, chronic obstructive pulmonary disease, inflammation, lung cancer

ABSTRACT

Patients with chronic obstructive pulmonary disease (COPD) are at increased risk of lung cancer, independently of smoking, although the link between these diseases remains unknown. Possible pathophysiologic mechanisms include inflammation and cellular senescence. COPD is a chronic inflammatory disease associated with secretion of numerous inflammatory mediators, many of which play a documented role in the promotion of cancer cell progression. COPD is also an age-related disease involving increased cellular senescence, an important hallmark of aging. Previous studies have confirmed the significant role of cellular senescence in the development of various tumors, including lung cancer. It is highly probable that cellular senescence contributes to carcinogenesis in COPD patients.

Introduction There is accumulating evidence confirming that chronic obstructive pulmonary disease (COPD) is a risk factor for lung cancer.[1] However, the mechanism linking the 2 diseases has not been fully elucidated. This review aims to present a novel insight into the common pathogenesis of COPD and lung cancer. We particularly focused on the new aspects of tumorigenesis in COPD patients, namely, inflammation as well as cellular senescence and aging.

Epidemiology of chronic obstructive pulmonary disease and lung cancer The increased risk of lung cancer in COPD patients was first described by Skillrud et al[2] in 1987, who showed that the 10-year cumulative risk of lung cancer was 8.8% for COPD patients, compared with 2.0% for controls. The prevalence of lung cancer in COPD patients varies between studies, depending on the study population, and hence on disease phenotype, severity of obstruction, age, other respiratory diseases, and smoking status (TABLE 1, FIGURE 1).[3-11] At the same time, numerous studies have shown that airway obstruction in COPD is associated with an increased risk of lung cancer, independently of smoking.[4,9,10] Calabro et al[11] documented that even mild obstruction, without a reduction in forced expiratory volume in 1 second, was a risk factor for lung cancer. Another independent indicator is the presence of emphysema on a low-radiation-dose computed tomography (CT) scan of the chest. Emphysema is associated with increased risk of lung cancer in individuals without airflow obstruction on spirometry, as well as those with coexistent airway obstruction and emphysema.[12,13] The results of multiple analyses investigating the link between COPD and lung cancer also differ depending on the type of study, from lung-cancer screening trials to population-based and case-control studies.[14,15] The causative role of COPD in lung cancer is supported by the finding that 40% to 70% of patients with lung cancer had clinically confirmed COPD that developed prior to cancer.[16-18] According to mortality studies, 20% to 30% of patients with COPD die from lung cancer.[19]

Prevention and early detection of lung cancer in patients with chronic obstructive pulmonary disease: screening programs and reducing exposure to risk factors Given that COPD favors carcinogenesis in the respiratory system, there is a need to

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Received: April 18, 2018.
Revision accepted: June 22, 2018.
Published online: August 31, 2018.
Conflict of interest: none declared.
Pol Arch Intern Med. 2018; 128 (7-8): 462-468
doi:10.20452/pamw.4297

TABLE 1 Prevalence of lung cancer in patients with chronic obstructive pulmonary disease in various studies

Study	No. of cases: COPD, controls (n); description of the study group	Odds of lung cancer in COPD patients, fully adjusted OR (95% CI)
Schwartz et al[3]	175, 81; women with combined obstructive lung disease classification	1.67 (1.15–2.41)
Koshiol et al[5]	509, 174	2.5 (2.0–3.1)
Powell et al[7]	2757, 2286	–
	404, 140; COPD diagnosis within 6 months	6.81 (5.49–8.45)
	199, 172; COPD diagnosis in 6–12 months	2.52 (2.00–3.19)
	1033, 947; COPD diagnosis in 1–5 years	2.48 (2.24–2.75)
	690, 580; COPD diagnosis in 5–10 years	2.68 (2.36–3.05)
	431, 447; COPD diagnosis ≥10 years	2.18 (1.87–2.54)
Denholm et al[8]	920, 647	–
	751, 577; only bronchitis	1.39 (1.21–1.59)
	77, 37; bronchitis and emphysema	1.70 (1.09–2.66)
	92, 33; only emphysema	2.68 (1.71–4.21)
Kishi et al[9]	19, 64	–
	8, 35; $FEV_1/FVC \times 100\%$ (61–70)	1.6 (0.5–5.6)
	4, 17; $FEV_1/FVC \times 100\%$ (51–60)	1.7 (0.4–7.4)
	7, 12; $FEV_1/FVC \times 100\%$ ≤50	4.1 (1.0–17.2)
Mannino et al[10]	54, 899	–
	16, 423; mild obstruction	1.4 (0.8–2.6)
	38, 476; moderate to severe obstruction	2.8 (1.8–4.4)
Calabro et al[11]	17, 839	1.23 (0.68–2.25)

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; OR, odds ratio

protect against lung cancer and to reduce the risk of its occurrence by decreasing exposure to harmful factors.

Multiple studies have confirmed the benefits of screening for lung cancer with low-dose CT in high-risk current and former smokers.[20] CT, when performed at intervals in COPD patients with a history of smoking, was associated with a higher detection rate of lung cancer and diagnosis at earlier stages.[21,22] The results of screening programs show that it is especially useful to implement screening procedures in emphysematous patients with severe obstruction and associated comorbidities.[23] The available evidence shows that CT screening can reduce lung cancer–specific mortality.[24] The screening programs prove to be better than other interventions, such as quitting smoking or treatment.[25] However, despite the numerous advantages, they are associated with the risk of false-positive results for small nodules, which must then be further evaluated.[26] Therefore, there is a need for developing newer methods that could identify patients with COPD and smoking history who are at risk of lung cancer.

Lung cancer screening scores based on body mass index, history of smoking, age, and emphysema or carbon monoxide diffusion capacity are easy-to-employ diagnostic tools for assessing the risk of lung cancer.[27] On the other hand, real-time elastography performed during endoscopic ultrasound, fluoroscopic-guided radial endobronchial ultrasound, chest ultrasound, and linear endobronchial ultrasound are more advanced procedures that may prove promising in the future.[28-31]

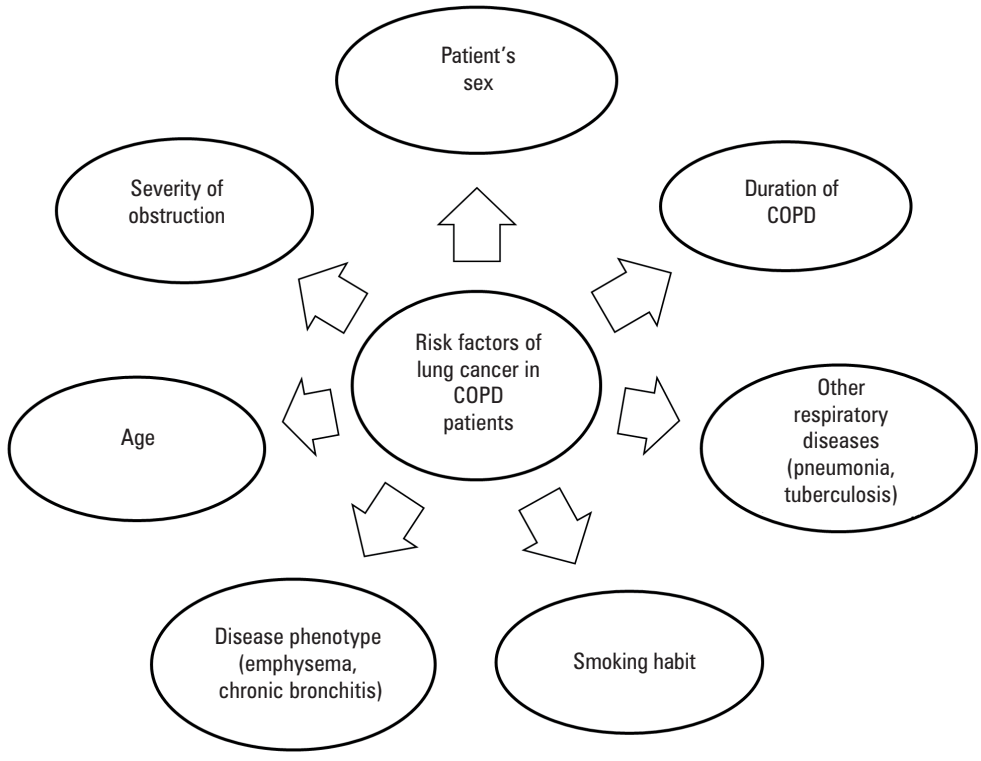

FIGURE 1 Risk factors of lung cancer in patients with chronic obstructive pulmonary disease (COPD)

Cigarette smoke and air pollution remain the most common risk factors of both COPD and lung cancer.[32,33] While cigarette smoke is responsible for even more than 90% of lung cancer cases, occupational exposure to particles, including carcinogens, such as polycyclic aromatic hydrocarbons, arsenic, nickel, and chromium, is associated with geographical region and is estimated to be responsible for 1% to 2% of lung cancer cases.[34]

A substantial body of evidence has confirmed the benefits of quitting smoking. In COPD patients who quit smoking, the risk of non–small cell lung cancer was reduced, although did not return to baseline.[35,36] The available data suggest that participation in screening programs increases the motivation to quit smoking, thus enhancing its effectiveness, which, however, is still quite low.[37] The positive results of low-dose CT also correlated with the maintenance of nicotine abstinence.[38] Regarding occupational exposure, air pollution prevention programs should be undertaken to reduce risk of smoking-dependent diseases, especially in urban areas.[39]

Inflammation in chronic obstructive pulmonary disease and its significance for promoting lung cancer A broad spectrum of different factors has been identified to be involved in tumorigenesis in COPD patients, including the deleterious activity of tobacco smoke, mutations, insufficiency of DNA repair mechanisms, and oxidative stress.[40] Interestingly, a common element linking all these agents is chronic tissue inflammation.[41] It is well known that inflammation that occurs in COPD results from chronic exposure to cigarette smoke, other risk factors, as well as aging.[42] Cigarette smoke induces the secretion of numerous inflammatory mediators, including lipids, free radicals, cytokines, chemokines, and growth factors, such as interleukin (IL)-1, IL-8, transforming growth factor (TGF)-β, and chemokine CCL21.[43,44] Many of these mediators have been shown to promote various mechanisms involved in multiple cancer cell progression.[45-47] They are also responsible for the major steps in lung cancer progression, including adhesion, migration, and proliferation. For example, IL-1β and tumor necrosis factor (TNF)-α, whose production is increased in COPD patients, have been found to induce the expression of adhesion molecules (eg, intercellular adhesion molecule 1 [ICAM-1]) in lung cancer cells and their more pronounced attachment to the vascular endothelium.[48] In addition, the adhesion of lung cancer cells has been linked to the expression and activity of multivalent extracellular matrix (ECM) constituents (fibronectin, type IV collagen) and their interactions with β1 integrins.[49,50] These interactions lead to phosphorylation of focal adhesion molecule, which, in turn, results in augmented cancer cell migration and proliferation. Lung cancer cell motility has also been stimulated by prostaglandin E2,[51] urokinase-type plasminogen activator receptor (uPAR/CD87),[52] Cdc42,[53] CYR 61,[53] claudin-1,[54] stromelysin-3,[55] matrix metalloproteinase (MMP)-2, MMP-7, and MMP-9,[56] CXCL12/SDF1,[57] and CCL21.[58,59]

Different cells are involved in the secretion of inflammatory molecules. Tertiary lymphoid aggregates created during inflammatory response to proteases and free radicals secreted by activated leukocytes may reflect lymphoid neogenesis, the first step of tumorigenesis, and could affect regulatory mechanisms, such as autophagy, apoptosis, angiogenesis, and cell repair.[60] Moreover, molecules secreted by T cells may also participate in tumorigenesis. An increase in the blood levels of Th2 cytokines (IL-4 and IL-10) was observed in patients with lung cancer, while those released by Th1 (IL-2 and interferon γ) were shown to decrease.[61] Additionally, myeloid-derived suppressor cells may affect T cells and regulate inflammation and carcinogenesis.[62]

Other cells that participate in tumorigenesis include macrophages. During tumor progression, macrophages are recruited to the site of cancer by a wide spectrum of chemoattractants, derived from the tumor and surrounding stroma. Once present in the tumor microenvironment, the macrophages can change their functional phenotype. At the early stage of cancer, tumor-suppressive M1 phenotype of macrophages occurs, which limits the progression of the malignancy. As tumorigenesis progresses, the macrophages acquire the tumor-promoting M2 phenotype, turning into the so called tumor-associated macrophages, and alter the microenvironment to support tumor development.[63-65]

Chronic obstructive pulmonary disease and cellular senescence of normal lung cells One of the functions of cellular senescence is to control the unlimited cell proliferation. In the 1960s, Hayflick and Moorehead[66] observed for the first time that cultured normal human cells undergo a limited number of divisions, after which they become senescent (FIGURE 2). This phenomenon was described as replicative senescence. In contrast, premature senescence occurs as the result of various endogenous and exogenous stressors, including oxidative stress, oncogene activation, and DNA damage.[67,68] Senescent cells change their morphology: they become bigger and flatter, contain more proteins, and their chromatin is reorganized. On becoming senescent, cells acquire an important ability to secrete a wide range of cytokines, chemokines, matrix remodeling proteases, and growth factors, which is referred to as senescence-associated secretory phenotype.[69] Moreover, senescence occurs not only in cells directly localized in the airways, but also in the microenvironment. The intercellular communication of senescent cells with normal neighboring cells has been described in previous studies.[70-72] Mikuła-Pietrasik et al[73,74] reported that senescent human peritoneal mesothelial cells can alter the secretory profile of ovarian cancer cells in a paracrine manner, supporting their invasiveness in the peritoneal cavity.

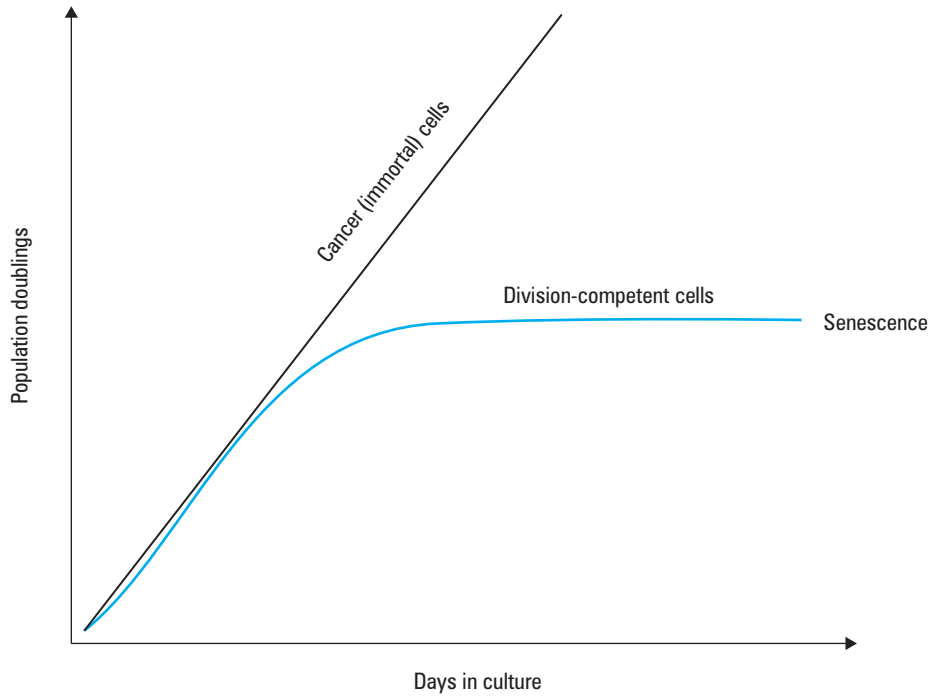

FIGURE 2 Hayflick phenomenon. Division-competent cells in culture will divide until they reach the limit of divisions, after which they become senescent.

Holz et al[75] were the first to discover cellular senescence in lung fibroblasts of patients with emphysema, confirming that the affected cells were less able to proliferate than cells from healthy volunteers. Subsequent studies documented the senescent-related phenotype in other cells from COPD patients, such as bronchial epithelial and endothelial cells.[76] Type II alveolar epithelial cells from the lung tissue of emphysematous patients showed reduced telomere length characteristic of replicative senescence.[76] Shortened telomeres were also seen in circulating leukocytes from COPD patients of various ages.[77,78] Similarly, reduced telomerase activity associated with cellular senescence and increased expression of cytokines has been described in the pulmonary endothelial cells of patients with COPD.[79]

Cellular senescence and the risk of cancer In recent years, it has been documented that the development of primary and metastatic tumors may be promoted by senescent cells that accumulate in vivo.[80,81] Senescent cells can produce multiple agents, including soluble signaling factors (interleukins, chemokines, and growth factors), secreted proteases, and secreted insoluble proteins and ECM components. This senescence-messaging secretome participates in the promotion of the most important processes associated with carcinogenesis, such as adhesion, proliferation, and migration. The frequency of cancer increases progressively with age, beginning at middle age. In general, the rate of cancer development is proportional to the rate of aging. This is certainly related to increased frequency of oncogenic mutations. It is less obvious, but widely documented, that the microenvironment is necessary to transform premalignant cells into invasive ones. For example, as shown by Krtolica et al,[82] senescent cells promote the growth of breast cancer cells in vitro and the development of solid tumors in vivo much more effectively than their younger counterparts. The same was observed for peritoneal mesothelial cells in which senescence appeared to stimulate ovarian, colorectal, and pancreatic cancer cell adhesion to a larger extent than in the case of young proliferating cells.[83,84]

It is well known that senescent cells, which accumulate in tissues in vivo, have several pro-oncogenic features. The most relevant feature is the ability to increase secretion of numerous soluble mediators involved in important processes in cancer spread, such as inflammation, angiogenesis, ECM remodeling, and the epithelial–mesenchymal transition. This hallmark of senescence is called senescence-associated secretory phenotype, and the mediators include cytokines (IL-1, IL-6, and IL-7),[85] chemokines (CXCL8/IL-8, CXCL12/SDF-1, CCL21/CCR7, and CXCL5/ENA-78),[58,86-88] growth factors (chemokine growth-regulated oncogene 1, heregulin β, vascular endothelial growth factor, TGF-β_1, connective tissue growth factor, hepatocyte growth factor, and fibroblast growth factor),[89,90] shed surface molecules (ICAM-1, uPAR, and TNF receptors),[84] and stromal ECM modulators (PAI-1, u-PA, MMP-2, and MMP-9).[91-93] Some of these agents are known to mediate various processes involved in lung tumorigenesis, such as proliferation (CXCL12 and CCL21), migration (CCL21), and invasion (CXCL5) (FIGURE 3).[58,94,95]

COPD and lung cancer are age-related diseases (FIGURE 4). Increased cellular senescence is one of the major indicators of aging.[96] There is growing evidence to support the presence of cellular senescence in COPD patients.[97] Its role in promoting invasiveness of many tumors, including lung cancer, has been widely confirmed. A role of cellular senescence in the overlap of COPD and

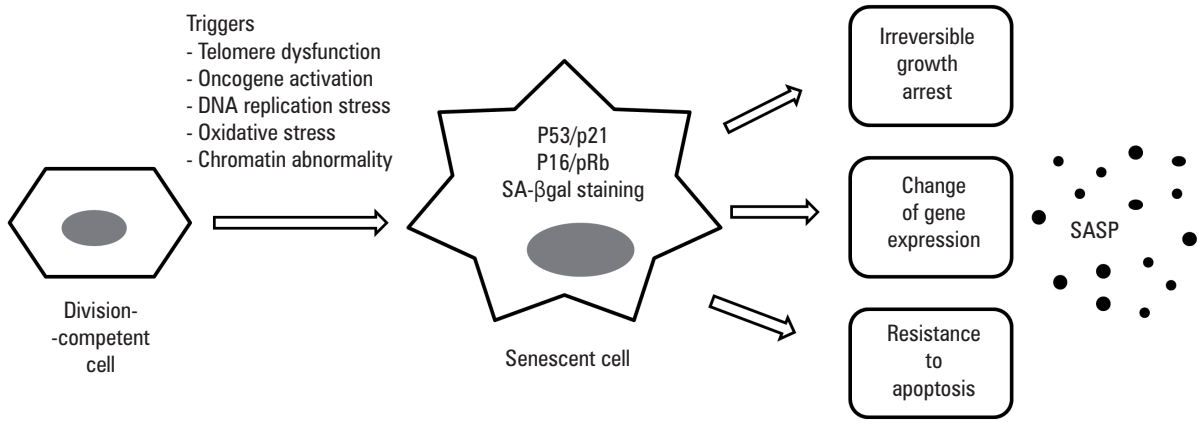

FIGURE 3 Characteristic features of cellular senescence. Division-competent cells, influenced by various triggers such as telomere detrition, oncogene activation, DNA replication stress, oxidative stress, and chromatin abnormality, change into senescent cells. Morphologically, senescent cells are bigger, flatter, contain more protein, and the chromatin undergoes reorganization. The characteristic features presented by cells undergoing senescence include involvement of the p53/p21 and p16/pRb pathways and an increase in senescence-associated β-galactosidase (SA-βgal), which can be seen on staining. Functional characteristics of senescent cells include irreversible growth arrest, resistance to apoptosis, and change of gene expression. Senescent cells display changes in their secretome, which is known as "senescence-associated secretory phenotype" (SASP).

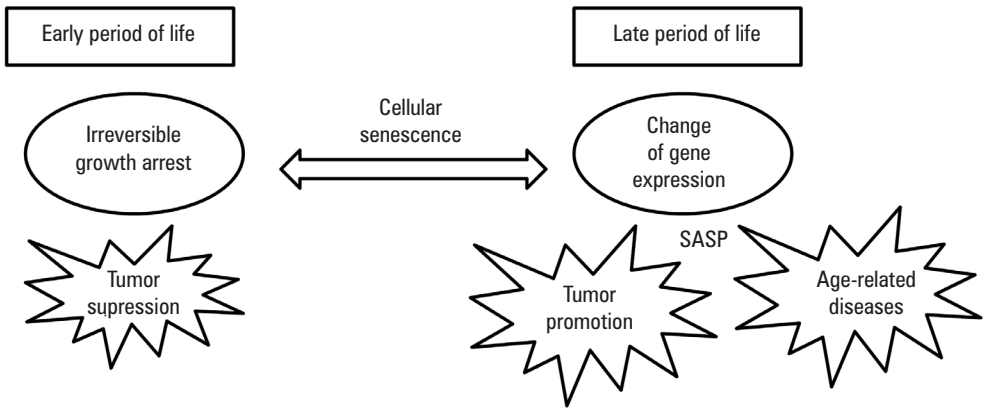

FIGURE 4 Antagonistic pleiotropy of senescence; emerging research highlights the participation of cellular senescence in the development of chronic obstructive pulmonary disease (which develops late in life and is treated as an age-related disease) and lung cancer. Abbreviations: SASP, senescence-associated secretory phenotype

lung cancer may suggest a common pathogenesis. More studies are needed to confirm the involvement of COPD-related cellular senescence in the tumorigenesis of lung cancer.

Conclusions Multiple studies confirm the crucial role of inflammation in the development of lung cancer in COPD patients. An increasing body of research has focused on cellular senescence in COPD patients. In the light of the current knowledge that cellular senescence may promote oncogenic activation, it seems that there is only one step to confirm its significance for lung cancer progression in COPD patients.

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