Senescence in Chronic Obstructive Pulmonary Disease

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There is a growing realization that chronic obstructive pulmonary disease involves several processes present in aging and cellular senescence. The impact of these processes in the pathogenesis of the main manifestations is multiple, particularly in the propagation of a proinflammatory phenotype, loss of reparative potential, and amplification of oxidative stress, all ultimately leading to tissue damage. This review highlights salient aspects related to senescence discussed in the 2011 Aspen Lung Conference.

Keywords: aging; senescence; oxidative stress; inflammation

Cellular senescence refers to a fundamental property of all cells to undergo cell growth arrest in the setting of cellular stresses (1). Teleologically, cell senescence can be viewed as a protection mechanism against cancer. The tumor suppressor systems coordinated by p53 and $p16^{Ink4A}$/Retinoblastoma are activated during these protective responses, largely accounting for the establishment of senescence (1). However, aging and cellular senescence underlie loss-of-function diseases, involving, for instance, the brain (e.g., Alzheimer's disease), cardiovascular system (atherosclerosis), and musculoskeletal system (e.g., osteoporosis).

Chronic obstructive pulmonary disease (COPD) caused largely by cigarette smoke exemplify how aging affects the lung, leading to tissue remodeling and alveolar destruction (2). In fact, age is an independent factor that relates to worse prognosis and disease progression (3). This led the 2011 Aspen Lung Conference organizers to include, for the first time, a state-of-the-art talk on cellular senescence, given by Judith Campisi (Buck Institute for Research on Aging, Novato, CA). As is apparent from the discussion that follows, cellular senescence is not only present in COPD lungs, but it can explain several of key features identified in the disease.

CELLULAR SENESCENCE IN COPD

Cigarette smoke was shown to induce expression of markers of senescence in lung epithelial cells and fibroblasts, including senescence-associated β-galactosidase (SA-βgal) (4, 5). These studies were further validated by the observations that emphysematous lungs show increased expression of senescence-associated cyclin kinase inhibitors (such as $p16^{Ink4a}$, $p19^{Arf}$, and $p21^{CIP1/WAF1/SDI1}$) (6, 7). In addition, further evidence on the potential role of p21 in experimental cigarette smoke–induced inflammation (8) has revealed novel pathways for potential therapeutic targeting (9).

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A key determinant of cellular senescence, telomere length, is also eroded in peripheral blood mononuclear cells (10, 11), which correlated both with smoking history and clinical severity. The mechanistic role of decreased expression of telomerase was underscored in the increased susceptibility to emphysema in mice lacking telomerase RNA template component (12). These findings are in line with the phenotype seen in mice lacking the telomerase reverse transcriptase component, which show overall alveolar simplification (13) and decreased lung regenerative potential (14).

What are key pathogenetic processes involved in COPD that are modulated by cell senescence? A clear implication is that senescent cells, notably progenitor cells, have decreased regenerative properties (15), potentially limiting the lungs' ability to recover after decades of injury caused by cigarette smoke. Perhaps the most important pathogenetic contribution of cellular senescence to the disease process is the enhancement of the inflammatory phenotype by cytokines released from senescent cells, which may underlie self-propagating processes in the COPD lung (16).

Chronic inflammation, such as that present in patients with COPD, may drive the aging process (17). Indeed, IL-6 and IL-8, two cytokines present in COPD lungs, can induce a maintenance of the senescent phenotype, that is, generate paracrine loops of cytokine secretion and activation of senescence in adjacent cells (18).

The release of approximately 80 factors in senescent cells underscores the "senescence-associated secretory phenotype" (SASP). These include cytokines, proteases, chemokines, and growth factors (17). Many of these factors have been linked to the pathogenesis of COPD, including IL-8, IL-6, IL-1 (19), and matrix metalloproteinase-1 (20).

The impact of senescent cells is manyfold. They can alter tissue structure and regeneration and may promote a favorable environment for cancer growth (17). This apparent paradox is hardly surprising: senescence may be a protective mechanism early in life, but of significant pathobiology after the age of procreation, enhancing the aging process (21) (the evolutionary aspect of lung destruction in COPD has been discussed in Reference 22.).

Senescence can be activated by DNA damage response, such as that induced by oxidative stress. Indeed, COPD lungs show macromolecular modifications indicative of oxidative stress (6), oxidative modifications of DNA (7), and DNA base modifications (23). Once activation of senescence occurs, the SASP phenotype is driven by transcription factors (NF-κB and C/EBPβ), the $p38^{MAPK}$ pathway, IL-1α, microRNAs, and chromatin reorganization (17). The latter allows for the concordant expression of clustered genes encoding family members of metalloproteases or cytokines, while the DNA remodels in large heterochromatin clusters called senescence-associated heterochromatin foci (SAHFs).

Although the evidence for an association between senescence and age-related organ dysfunction is strong, the cause–effect

relationship between these events is relatively sparse. More conclusive evidence has been provided, in which deletion of cells expressing $p16^{Ink4a}$ alleviated age-related pathologies in adipose, muscular, and optic tissues of the BubR1 progeroid mouse background (24). At the present time, a pathophysiological role for cell senescence in COPD has not been conclusively shown. A step toward validating this hypothesis has been uncovered in a report that senescent pulmonary artery smooth cells may participate in pulmonary vascular dysfunction and pulmonary hypertension in COPD due to the SASP phenotype (25). Nevertheless, the data in this study are mostly correlative, with functional insights presented in cultured cells. Conclusive mechanistic data will require genetic manipulations in animal models with deletion or enhancement of cell senescence (as in the BubR1 mice) and pharmacological interventions that halt the senescence process.

CONCLUSIONS

There is compelling evidence that lung aging participates in COPD, potentially amplifying destructive processes and accounting for the mortality and morbidity of the disease. The elucidation of the precise pathogenetic role of senescence will require extensive mechanistic investigations. The role of senescence is probably cell specific, as both type II and endothelial cells express markers of senescence in emphysematous lungs. Autophagy, which is also linked to senescence and participates in cigarette smoke–induced lung injury (26), may modify the contribution of senescence to COPD. These fascinating questions remain for discussions in future Aspen Lung Conferences. The 54th edition of the conference introduced aging and senescence, which will become ever more important aspects of COPD research.

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