Senescence, the Janus of Lung Injury and Repair

Janus, the old Roman mythological god of transitions and duality, was represented by two distinct faces: youth and aging, or, alternatively, as the beginning and the end. Senescence has been described as an essential mechanism of cell differentiation and organ formation during embryogenesis (1) and organ repair in younger individuals (2, 3). However, with age, we observe an accumulation of senescent cells in different organs, including the lung. This increases the susceptibility for developing chronic lung diseases, such as chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis (IPF), and also increases the risk of frailty and death as a final consequence (4–6).

IPF is an age-related lung disease associated with abnormal accumulation of senescent cells, including lung fibroblasts and myofibroblasts, that promote deposition of the extracellular matrix, altering the blood–gas barrier and consequently obstructing gas exchange. The processes leading to unremitting fibroblast accumulation in IPF are only partially understood. Thus, there is an urgent need to elucidate mechanisms by which senescent IPF lung fibroblasts accumulate, constrain the capability of tissue regeneration, and result in lung disrepair or fibrosis. Notably, the prognosis for patients with IPF in most cases is poor, with a mean survival of only 2.5–3 years.

It has been known for some time that IPF fibroblasts are larger, resistant to apoptosis, and metabolically active. Recently, it has been recognized that IPF lung fibroblasts are senescent cells (7) that express several inhibitors of the cell cycle, including p21 and p16, that inhibit CDKs (cyclin-dependent kinases) 2 and 4/6, respectively, and that express a large variety of soluble factors in a behavior known as the senescence-associated secretory phenotype. In this issue of the *Journal*, Kato and colleagues (pp. 633–644) report that, once the myofibroblast becomes senescent, this is a one-way cell dedifferentiation response, which also results in apoptosis resistance, a distinctive characteristic of senescent cells (8). This is a critical finding that may, in part, explain why fibrosis in aged subjects is irreversible.

In the study, the authors define senescent IPF lung myofibroblasts as exhibiting a myogenic differentiation factor (MyoD)-mediated impaired capacity for dedifferentiation and physiological proliferation along with resistance to apoptosis. In contrast, control cells, in which the transcription factor, MyoD, decreases, undergo dedifferentiation, proliferate, and are subsequently more susceptible to apoptosis. In addition, they demonstrate that MyoD was highly expressed and critical for inhibiting dedifferentiation and for promoting persistent fibrosis in the lungs of aged mice and in the lungs of patients with IPF. This supports the concept that the plasticity of myofibroblasts may be critical for normal physiologic versus pathologic responses after tissue injury. The same group has previously shown, using a bleomycin-induced lung fibrosis model in young mice where fibrosis resolves, that senescence of fibroblasts is reversible, as is their accumulation. In contrast, in the bleomycin-treated aged mice, as is the case in IPF, senescence is prolonged and persistent. Indeed, several studies by members of this group confirmed that the apoptosis resistance of myofibroblasts contributes to persistent, nonresolving IPF fibrosis (9–11).

The mechanisms underlying the accumulation of senescent fibroblasts, and their role in evolution/resolution of fibrosis in young mice versus persistent accumulation in aged mice that do not resolve fibrosis, have been poorly understood. The study by Kato and colleagues now implicates dedifferentiation and the subsequent apoptosis resistance as critical mechanisms by which myofibroblast senescence may contribute to persistent fibrosis in aging. Senescence was originally described as an intrinsic cellular mechanism protecting against tumor development. Upon abnormal stimulation of oncogenes, healthy cells—including fibroblasts—can undergo cellular senescence and cell cycle arrest, thereby functioning as an essential barrier against tumor development *in vivo* (12). More recently, senescence has been identified as part of the normal process of organ repair. In young individuals, senescent cells were shown to be subject to immune-mediated clearance, showing that senescence surveillance is essential for the antifibrotic mechanism *in vivo* through the clearance of profibrotic lung fibroblasts (13), which promotes the resolution of fibrosis (14).

Important mechanistic aspects remain unsolved, and are relevant to the development of new therapies. Questions that are generated from the present work include: How does MyoD negatively regulate apoptosis? Is TGF (transforming growth factor)-β the only mechanism implicated in the increase in the expression of MyoD? Is MyoD a p53-dependent mechanism of cellular senescence? These questions still need to be addressed. An alternative explanation to their main observation is that the differences observed in the levels of MyoD expression in IPF myofibroblasts and healthy control cells may be the result of defects in lysosomes or the ubiquitin–proteasome pathway of protein degradation, which could also affect the persistence of MyoD expression.

In summary, evidence suggests that young cell senescence and senescence surveillance are essential components of organ development, repair, and antitumor defense. Accumulation of senescent cells may promote fibrosis in aged organisms by secreting soluble factors, senescence-associated secretory phenotypes, that contribute to the onset of senescence in neighboring cells through paracrine transmission, and by altering the surrounding environment by the secretion of extracellular matrix proteins (15). We anticipate that strategies targeting apoptosis of dedifferentiated senescent lung fibroblasts holds great promise for improving the prevention of and therapy for fibrosis. ■

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