PAI-1: A New Target for Controlling Lung-Cell Senescence and Fibrosis?

The pathogenesis of fibrosis in different organs remains to be clearly defined, although there is a consensus that fibrogenic processes share common mechanisms at the molecular level. Both an increased rate of collagen synthesis and a decreased rate of collagen degradation promote fibrosis (1). These two distinct aspects correspond well to two pivotal fibrogenic factors: transforming growth factor β (TGF-β), which can induce the differentiation of various cell types into activated myofibroblasts, and PAI-1 (plasminogen activator inhibitor-1, also called serpine1), the well-known inhibitor of fibrin degradation, whose overexpression contributes to the accumulation of extracellular matrix (1). Both TGF-β and PAI-1 are upregulated in the fibrotic lung, and alveolar type II (ATII) cells are an important source for the synthesis and release of these factors (2, 3).

One cellular mechanism responsible for excessive release of TGF-β and PAI-1 is the process of cell senescence. Cell senescence is defined as a stable arrest of proliferation with the acquisition of a specific senescence-associated secretory phenotype (SASP) characterized by the production of proinflammatory cytokines, immune modulators, metalloproteases, and profibrotic molecules, including TGF-β and PAI-1 (4–7). Proof that lung-cell senescence induces lung fibrosis comes from the observation that a substantial proportion of individuals who exhibit accelerated cell senescence due to a mutation in the *TERT* (telomerase reverse transcriptase) gene develop lung fibrosis (8). A molecular link thus exists between cell senescence and lung fibrosis, as both TGF-β and PAI-1, two well-established components of the SASP, are fibrogenic. The release of these two factors, notably PAI-1, is so characteristic of senescent cells that it is used as a validated marker of cell senescence, irrespective of cell type and/or the mechanism responsible for cell senescence (4).

In this issue of the *Journal*, Rana and colleagues (pp. 319–330) extend their previous work (2) and report the novel finding that PAI-1 in the fibrotic lung acts not only as a fibrogenic factor but also as a strong inducer of cell senescence, notably of ATII cells (9). The fact that PAI-1 can serve as both a marker and a promoter of cell senescence was initially demonstrated by Kortlever and colleagues *in vitro* (10). In their studies, overexpressed PAI-1 was sufficient to induce replicative fibroblast senescence, even in the absence of p53. The role of PAI-1 as a mediator of cell senescence was subsequently extended to other cell types, including keratinocytes and vascular cells, with strong arguments for an *in vivo* role of this mechanism in inducing senescence of the cardiovascular system (11).

The present work by Rana and colleagues, together with their previous studies (2), provides incontrovertible evidence that PAI-1 is also a strong mediator of ATII-cell senescence, acts in concert with TGF-β, and has a role in this pathway that is highly relevant to the process of lung fibrosis, whether induced experimentally or developing in patients with idiopathic pulmonary fibrosis (IPF). Previous work by this team showed that PAI-1 could activate p53 and mediate bleomycin- and doxorubicin-induced ATII-cell senescence both *in vitro* and *in vivo* (2). Of note, PAI-1 deletion in mice suppressed bleomycin-induced ATII cell senescence and attenuated lung fibrosis. In their current study, Rana and colleagues further buttress this concept by showing that TGF-β can behave as an inducer of ATII-cell senescence, and that its prosenescent effects are mediated by PAI-1. TGF-β is well known to upregulate PAI-1 via several signaling pathways, with one potential consequence being entry into a cell-senescence program. This effect, however, may be highly dependent on the target cell, as PAI-1 seems to have completely opposite effects on fibroblasts and ATII cells in patients with IPF (3). Thus, fibroblasts from patients with IPF have a low expression of PAI-1 and exhibit increased cell proliferation in response to TGF-β, and these changes are reversed by restoration of PAI-1 expression (3). Which of these mechanisms may account for the final effect of PAI-1 in the IPF lung remains to be determined in further investigations.

The results obtained by Rana and colleagues with ATII cells suggest that ATII-cell senescence and PAI-1 release might be part of a vicious cycle in which both phenomena, while being activated, interact with each other, ultimately exerting a strong cumulative and synergistic effect that is responsible for lung fibrosis and remodeling of the lung parenchyma. Additional *in vivo* studies are needed to determine which event occurs first in a given condition. We know that bleomycin, as a strong inducer of DNA damage, is also a potent inducer of cell senescence. Genetic elimination of senescent cells in the bleomycin model attenuates lung fibrosis (12) similarly to PAI-1 inactivation (13, 14). Whether the elimination of senescent cells and inactivation of PAI-1 produce additional effects is a question of considerable interest. Indeed, it remains to be determined whether the fibrogenic activity of PAI-1 can be considered independently of the process of cell senescence, whether PAI-1 needs induction of cell senescence to exert its fibrogenic activity, and whether PAI-1 works in a cooperative manner with other actors related to senescent cells.

A result of great interest reported by Rana and colleagues is that either pharmacological PAI-1 inhibition or PAI-1 gene deletion blocked TGF-β–induced ATII-cell senescence and SASP development. Moreover, subsequent alveolar macrophage activation was blunted. This evidence that PAI-1 is a druggable target is of major importance, given the growing focus of

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pharmaceutical research on developing drugs that target senescent cells. Two main strategies that are under scrutiny at present involve the use of senolytics, which are toxic to senescent cells and expected to produce beneficial effects via senescent-cell elimination, and senomorphics, which counteract the cell-senescence process. The latter strategy is of particular value given the variety of cell-senescence programs that are involved in different pathologies. Targeting one specific cell-senescence–mediating pathway in a given disease may be viewed as ideal. The results reported by Rana and colleagues suggest that lowering PAI-1 expression and/or activity may constitute such an ideal approach to the control of lung fibrosis. ■

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References

1. Ghosh AK, Vaughan DE. PAI-1 in tissue fibrosis. *J Cell Physiol* 2012;227: 493–507.
2. Jiang C, Liu G, Luckhardt T, Antony V, Zhou Y, Carter AB, *et al*. Serpine 1 induces alveolar type II cell senescence through activating p53-p21-Rb pathway in fibrotic lung disease. *Aging Cell* 2017;16: 1114–1124.
3. Marudamuthu AS, Shetty SK, Bhandary YP, Karandashova S, Thompson M, Sathish V, *et al*. Plasminogen activator inhibitor-1 suppresses profibrotic responses in fibroblasts from fibrotic lungs. *J Biol Chem* 2015;290:9428–9441.
4. Kumar M, Seeger W, Voswinckel R. Senescence-associated secretory phenotype and its possible role in chronic obstructive pulmonary disease. *Am J Respir Cell Mol Biol* 2014;51:323–333.
5. Coppé JP, Desprez PY, Krtolica A, Campisi J. The senescence-associated secretory phenotype: the dark side of tumor suppression. *Annu Rev Pathol* 2010;5:99–118.
6. Tchkonia T, Zhu Y, van Deursen J, Campisi J, Kirkland JL. Cellular senescence and the senescent secretory phenotype: therapeutic opportunities. *J Clin Invest* 2013;123:966–972.
7. Adnot S, Amsellem V, Boyer L, Marcos E, Saker M, Houssaini A, *et al*. Telomere dysfunction and cell senescence in chronic lung diseases: therapeutic potential. *Pharmacol Ther* 2015;153: 125–134.
8. Alder JK, Chen JJ, Lancaster L, Danoff S, Su SC, Cogan JD, *et al*. Short telomeres are a risk factor for idiopathic pulmonary fibrosis. *Proc Natl Acad Sci USA* 2008;105:13051–13056.
9. Rana T, Jiang C, Liu G, Miyata T, Antony V, Thannickal VJ, *et al*. PAI-1 regulation of TGF-β1–induced alveolar type II cell senescence, SASP secretion, and SASP-mediated activation of alveolar macrophages. *Am J Respir Cell Mol Biol* 2020;62: 319–330.
10. Kortlever RM, Higgins PJ, Bernards R. Plasminogen activator inhibitor-1 is a critical downstream target of p53 in the induction of replicative senescence. *Nat Cell Biol* 2006;8:877–884.
11. Vaughan DE, Rai R, Khan SS, Eren M, Ghosh AK. Plasminogen activator inhibitor-1 is a marker and a mediator of senescence. *Arterioscler Thromb Vasc Biol* 2017;37:1446–1452.
12. Schafer MJ, White TA, Iijima K, Haak AJ, Ligresti G, Atkinson EJ, *et al*. Cellular senescence mediates fibrotic pulmonary disease. *Nat Commun* 2017;8:14532.
13. Bauman KA, Wettlaufer SH, Okunishi K, Vannella KM, Stoolman JS, Huang SK, *et al*. The antifibrotic effects of plasminogen activation occur via prostaglandin E2 synthesis in humans and mice. *J Clin Invest* 2010;120:1950–1960.
14. Senoo T, Hattori N, Tanimoto T, Furonaka M, Ishikawa N, Fujitaka K, *et al*. Suppression of plasminogen activator inhibitor-1 by RNA interference attenuates pulmonary fibrosis. *Thorax* 2010;65: 334–340.