The STATus of STAT3 in Lung Cell Senescence?

Exaggerated lung-cell senescence is now emerging as a key pathogenic factor in several chronic age-related respiratory disorders, including lung fibrosis and chronic obstructive pulmonary disease (COPD) (1–3). In both diseases, exaggerated lung-cell senescence may result from a combination of replicative cell senescence due to telomere shortening and premature cell senescence caused by stress stimuli such as oxidative stress and inflammatory mediators. Targeting cell senescence may hold therapeutic promise in these diseases (4, 5). The challenge is to identify molecular pathways involved in lung-cell senescence that could be targeted pharmacologically.

The work by Waters and colleagues (pp. 61–73) in this issue of the *Journal* identifies STAT3 as a transcription factor potentially involved in oxidant-induced senescence of human lung fibroblasts (6). In previous work by these authors, lung STAT3 activity was strongly associated with progression of idiopathic pulmonary fibrosis (IPF) (7). In this study, STAT3 activation coincided with cell senescence induction by H_2O_2 exposure, and inhibition of STAT3 reduced the number of β-galactosidase$^+$ senescent cells. STAT3 blockade decreased certain cell-senescence markers but was not assessed for its ability to reverse the stable cell proliferation arrest. STAT3 activation by low H_2O_2 concentrations was recently shown to involve a redox-relay system mediated by peroxiredoxin-2 (Prdx2) (8). Prdx2 is easily oxidized by H_2O_2 and then oxidizes and activates STAT3. Conceivably, interference with this relay system might prevent or reverse STAT3 activation; if so, this would identify a new redox signaling paradigm with potential relevance for cell-senescence induction in lung diseases. Interestingly, phosphorylated STAT3 seemed to translocate not only to the nucleus, as expected, but also to the mitochondria. Confirmation of this possibility will require additional experimental approaches such as confocal microscopy, subcellular fractionation, and examination of larger numbers of samples. However, blocking STAT3 attenuated the mitochondrial dysfunction associated with senescence in the model used. These results identifying STAT3 as one of the potential drivers of oxidative stress-induced cell senescence are consistent with crucial roles for both mitochondrial dysfunction and oxidative damage in IPF and COPD. Further studies are therefore needed to determine whether STAT3 inhibition attenuates the senescence of fibroblasts derived from lungs of patients with IPF, which exhibit accelerated senescence when studied *in vitro* (9).

An important issue raised by these findings is whether STAT3 might be a better target than its upstream activators. STATs, which are JAK/STAT pathway effectors, are considered to be among the architecturally simplest transmembrane receptor-to-nucleus communication systems (10). They are known to be activated by a wide variety of cytokines, growth factors, and hormones. STAT3 is a latent cytoplasmic transcription factor that can couple with multiple cytokines and growth factor receptors, such as the gp130/IL6 receptor, vascular endothelial growth factor, platelet-derived growth factor, and G protein–coupled receptor ligands (10, 11). Selective JAK activation by different receptors produces different *in vivo* effects. Consequently, targeting a specific receptor upstream of the pathway (JAK or STAT) may have different effects, notably on the senescence program. The mechanisms upstream of STAT3 activation must therefore be investigated in different lung-cell types in fibrotic lung tissues from human patients and experimental animals.

Extensive JAK/STAT pathway studies in aging have demonstrated that this pathway plays a major role in regulating cytokine production as part of the senescence-associated secretory phenotype (SASP). Previous studies established that JAK activation mediates the SASP in adipose cells during aging (12). JAK1/2 inhibitors reduced inflammation and alleviated frailty in aged mice (12). Until now, the search for means of blocking the JAK/STAT pathway has focused on JAK because selective and nonselective JAK1/2 inhibitors are available and used clinically (10). Here, Waters and colleagues show that targeting STAT3, in addition to inhibiting certain SASP components, protected against cell senescence (6). Targeting JAK1/2 or STAT3 may therefore produce different effects. Support for this possibility comes from the ability of STAT to be activated not only by JAK but also by the mitogen-activated protein kinase pathway (10). Moreover, a previous study showed that transforming growth factor-β stimulation of lung fibroblasts resulted in SMAD2/SMAD3-dependent phosphorylation of STAT3 (13). Further support for directly targeting STAT3 can also be found in that study, which showed that the small-molecule STAT3 inhibitor C-188-9 decreased pulmonary fibrosis in the mouse bleomycin model (13). Moreover, STAT3 has been shown to contribute to pulmonary fibrosis through epithelial injury and fibroblast–myofibroblast differentiation, as well as to epithelial cell differentiation (13, 14).

Another issue raised by these findings is whether STAT3 activation is relevant only to the lung-cell senescence program involved in the pathogenesis of IPF or also plays a role in other lung diseases such as COPD and emphysema. A causal relationship between cell senescence and the lung manifestations of lung fibrosis or COPD has been firmly established by reports that individuals carrying a telomerase TERT gene mutation develop either lung fibrosis or lung emphysema, or both (15, 16). However, the reasons underlying the differences among these disease phenotypes are unknown. They may relate to the cell types involved, differences

in cell-senescence programs, or specific molecular senescence mechanisms that promote specific lung pathologies. An increase in JAK/STAT was previously demonstrated in lungs from patients with COPD, although its role was not investigated (17). Moreover, JAK/STAT pathway activation has been reported in nonpulmonary age-related diseases (12).

Thus, identification of master signaling pathways involved in cell-senescence programs in IPF and COPD is urgently needed to better understand how senescent cells contribute to these diseases and to better define molecular targets for future targeted therapies. ■

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