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REVIEW

Fibroblast senescence in the pathology of idiopathic pulmonary fibrosis

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Waters DW, Blokland KE, Pathinayake PS, Burgess JK, Mutsaers SE, Prele CM, Schuliga M, Grainge CL, Knight DA. Fibroblast senescence in the pathology of idiopathic pulmonary fibrosis. *Am J Physiol Lung Cell Mol Physiol* 315: L162–L172, 2018. First published April 26, 2018; doi:10.1152/ajplung.00037.2018.—Idiopathic pulmonary fibrosis (IPF) is a chronic fibrosing interstitial pneumonia of unknown cause with a median survival of only three years. Little is known about the mechanisms that precede the excessive collagen deposition seen in IPF, but cellular senescence has been strongly implicated in disease pathology. Senescence is a state of irreversible cell-cycle arrest accompanied by an abnormal secretory profile and is thought to play a critical role in both development and wound repair. Normally, once a senescent cell has contributed to wound repair, it is promptly removed from the environment via infiltrating immune cells. However, if immune clearance fails, the persistence of senescent cells is thought to drive disease pathology through their altered secretory profile. One of the major cell types involved in wound healing is fibroblasts, and senescent fibroblasts have been identified in the lungs of patients with IPF and in fibroblast cultures from IPF lungs. The question of what is driving abnormally high numbers of fibroblasts into senescence remains unanswered. The transcription factor signal transducer and activator of transcription 3 (STAT3) plays a role in a myriad of processes, including cell-cycle progression, gene transcription, as well as mitochondrial respiration, all of which are dysregulated during senescence. Activation of STAT3 has previously been shown to correlate with IPF progression and therefore is a potential molecular target to modify early-stage senescence and restore normal fibroblast function. This review summarizes what is presently known about fibroblast senescence in IPF and how STAT3 may contribute to this phenotype.

fibroblast senescence; idiopathic pulmonary fibrosis; signal transducer and activator of transcription 3

INTRODUCTION

The interstitial lung diseases (ILDs) are a broad group of clinically defined lung disorders that are characterized by remodeling of the parenchyma and alveolar space through the chronic accumulation of extracellular matrix (ECM). This accumulation permanently inhibits oxygen transfer, leading to the characteristic symptoms of shortness of breath and exercise limitation and the clinical signs of fine basal inspiratory crackles on auscultation. Many ILDs have identifiable causes, such as inhaled proteins leading to hypersensitivity pneumonitis and drug therapies, including cancer chemotherapy; however, the causes of the majority of ILDs remain unknown. The most common disease in this group is idiopathic pulmonary fibrosis (IPF), affecting at least five million people globally and carrying with it a poor prognosis, with a median survival of three years, which is shorter than many cancers (87). Because of a greater understanding of the disease, advances in detection techniques, and an aging population, the incidence of IPF is increasing globally (34, 45).

Common risk factors for IPF include male sex (23, 37, 46), older age, with two-thirds of patients over 60 years of age at

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diagnosis (49, 86), and, interestingly, a history of cigarette smoking (6). Occupational exposures and gastroesophageal reflux (GERD) have been associated with the disease; the risk of developing IPF after metal and wood dust exposure increases proportionally with the number of years of exposure (6), whereas GERD is associated but not yet causally linked to the disease (reviewed in Ref. 31). All of the recognized risk factors for IPF share the ability to disrupt the lung epithelium once inhaled, which suggests that chronic respirable insults are sufficient to initiate the pathological changes of IPF in susceptible individuals.

Offsetting the dismal prognosis for people with IPF, two drugs (nintedanib and pirfenidone) have been shown to slow disease progression, reduce the decline in forced vital capacity, and increase longevity. As a result, in 2014, both were awarded FDA "breakthrough" designation and fast-track registration (50, 89). Nintedanib is a tyrosine kinase inhibitor, targeting receptors for vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF), all of which are involved in transmembrane signaling and signal transduction (87). Tyrosine kinases play critical roles in the pathogenesis of IPF, with patients with IPF having an altered expression of specific tyrosine kinases that stimulate the migration and proliferation of lung fibroblasts (35, 61). The precise mode of action of pirfenidone remains unclear, predominantly because of its potential to exert an effect on numerous aspects of fibrosis. One decisive factor in the action of pirfenidone is thought to be its capacity to posttranscriptionally inhibit inflammatory cytokines and to enhance production of the anti-inflammatory cytokine interleukin-10 (IL-10) (73). Conclusions from the original patent application suggested that pirfenidone inhibits PDGF- and FGF-stimulated fibroblast proliferation and transforming growth factor-β (TGF-β)-stimulated procollagen synthesis from stromal cells (63).

Although these drugs only slow the relentless progression of the disease, they have demonstrated a survival benefit (90) and hence unequivocally demonstrated that IPF is treatable. However, neither drug reverses established fibrosis, and the majority of patients continue to decline, with lung transplant remaining the only definitive treatment.

IPF PATHOLOGY

The pathogenesis of IPF is proposed to occur as a result of repeated inhaled stimuli causing sequential injury to the lung epithelium (97). These injurious events are thought to result in disruption of the alveolar-capillary basement membrane, followed by excessive ECM deposition and fibrosis in the lung parenchyma (for a review of ECM in lung disease, see Ref. 11). In an IPF lung, fibrosis is typically heterogeneous with areas of relatively normal lung lying adjacent to areas of dense fibrosis (87). Despite this spatial heterogeneity, the fibrosis is thought to emanate from the parenchyma of the lower lobes (87).

Although little is known about the mechanisms that ultimately result in the excessive collagen deposition in IPF, cellular senescence has recently been strongly implicated in disease pathology. Cellular senescence is a state of cell-cycle arrest accompanied by an abnormal secretory profile, and, although in nonpathological states senescence is an important cellular pathway fundamental to embryonic development (71, 101) and preventing malignancies (17, 114), senescent cells are not a permanent feature in healthy tissue. In wound healing, for example, senescent fibroblasts appear early on in the stages of wound resolution, where they accelerate wound closure by inducing the differentiation of cells through their altered secretory profile (28).

Present understanding of IPF suggests that the disease is an interaction of genetic susceptibility, aging-associated processes, and repeated microinjury. The summation of these processes may affect certain cell types more substantially than others, with present evidence pointing toward fibroblasts and epithelial cells being primarily affected. This review will focus on the role of fibroblast senescence in the pathology of IPF.

The influence of the role of signal transducer and activator of transcription 3 (STAT3) in the acquisition of the senescent phenotype will also be explored in light of the numerous cellular processes that STAT3 regulates. STAT3 is a latent transcription factor, the activation of which is largely dependent on the IL-6 family of cytokines. Activation of STAT3 initiates the transcription of many of the factors that characterize the altered secretory profile of senescent cells, influences cell-cycle progression, and also plays a central role in mitochondrial respiration.

SENESCENCE

The senescent phenotype was first recognized in 1961 by Hayflick and Moorhead (40), who described the finite proliferative potential of fibroblasts in vitro. Fibroblasts underwent a limited number of population doublings before entering a state of permanent growth arrest, the gradual exhaustion of the replicative potential of cells now recognized as replicative senescence (RS). Since their discovery, senescent cells have been identified in embryological organs that are evolutionarily conserved through all the major animal lineages, suggesting that the phenotype is ancient (71, 93, 101).

RS is considered in mitotic time as opposed to metabolic time; this is to say that it is not necessarily the chronological age of a cell that influences its path into senescence but rather the number of cell divisions. Senescent cells exhibit a blunted response to mitogenic stimuli (107), undergo growth arrest (16), and display increased activity of senescence associated-β-galactosidase (SA-β-Gal) (29).

In vitro, the telomeres of human somatic cells shorten by 30–200 bp with each mitotic event (39), and their specific role in conjunction with associated proteins is to prevent damage to the genome attributable to the "end replication problem." The gradual degradation of telomeres, attributable to mitosis, ultimately results in a critical limit that is unable to effectively protect the DNA. Insufficient telomere length is thought to manifest in an increase in the incidence of double-strand breaks (DSBs) at the DNA ends. Activation of the p53 pathway is a common cellular response to DNA double-strand breaks, and, as a result, downstream targets of p53, including the cyclin-dependent kinase inhibitors $p21^{waf1}$ and $p16^{ink4D}$, serve as markers of senescence (84).

Although senescent cells do not undergo cell division, importantly, they remain viable and metabolically active (12, 32). It is this feature that is central to the proposed role of senescent cells in the pathogenesis of IPF, developing what has been

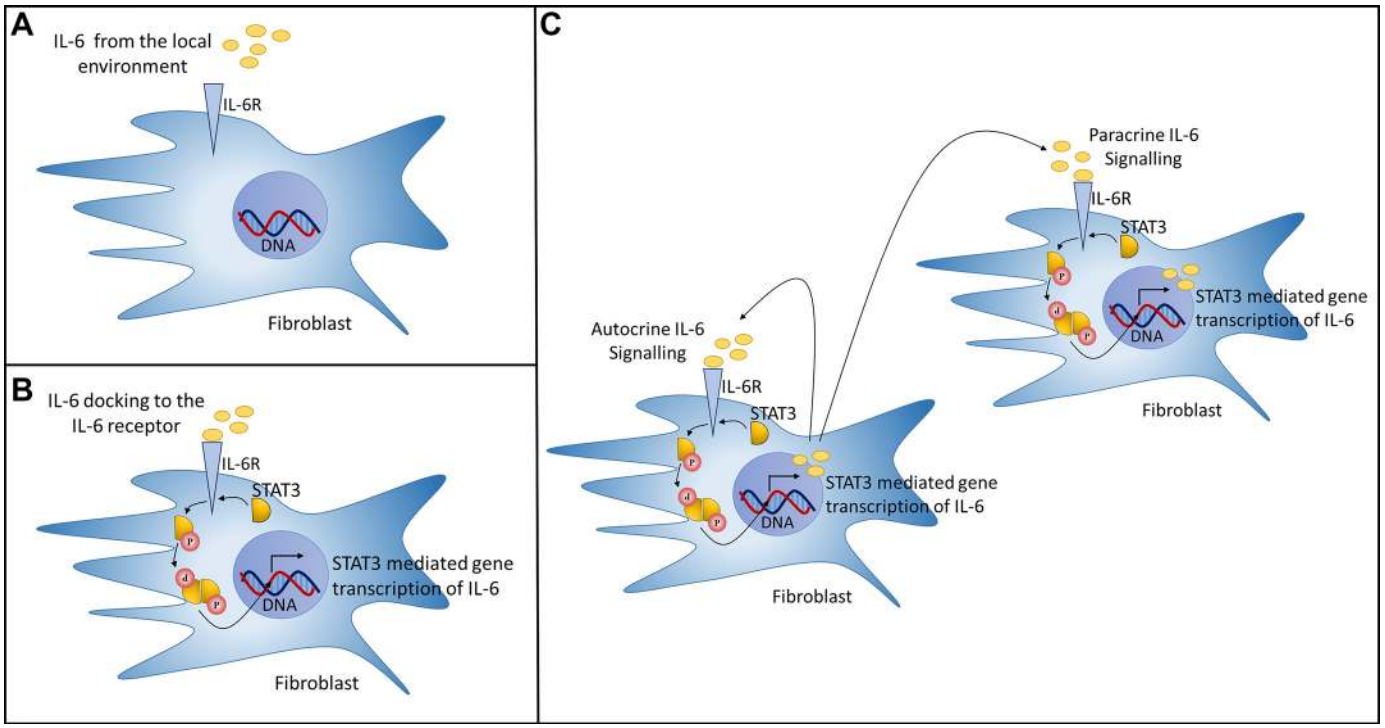

Fig. 1. A scenario of cytokine-stimulated gene transcription mediated by the signal transducer and activator of transcription 3 (STAT3) activation pathway is shown. One of the core factors of the altered secretory profile of senescent fibroblasts is the cytokine IL-6, a major activator of the STAT3 pathway. *A*: IL-6 binding to the IL-6R on the fibroblast surface initiates an activation cascade. *B*: STAT3 recruitment to Janus kinase 1 (JAK) (not shown), a nonreceptor tyrosine kinase, results in STAT3 phosphorylation, dimerization, and translocation to the nucleus to mediate the transcription of target genes. *C*: persistent feedback loop potentially influencing autocrine and paracrine signaling has been identified where by STAT3-mediated transcription of sphingosine-1-phosphate receptor-1 (S1PR1) induces pSTAT3 through Jak2 activation (55). This positive feedback loop is thought to constituently activate STAT3, upregulating IL-6 transcription, ultimately resulting in its release to the local environment. A negative feedback mechanism for STAT3 does exist and is mediated by the suppressors of cytokine signaling (SOCS) proteins (118); however, loss of this negative feedback loop has been shown to be a feature of disease (4), and the SOCS/STAT3 silencing mechanism has also been reported to be diminished in idiopathic pulmonary fibrosis-derived fibroblasts (83).

described as the senescence-associated secretory phenotype (SASP) (21). The SASP plays important physiological roles and mediates several processes, such as cellular differentiation during wound repair. However, because of the characteristic secretory signature of the SASP, its persistence in the environment may contribute to the pathology of IPF through autocrine and paracrine interactions, such as cytokine-stimulated gene transcription (Fig. 1). The transcription factor NF-κB has increased activity with aging and aging-related chronic diseases (104) and has been shown to act as a regulator of the SASP, influencing the expression of more senescence-associated genes than p53 (18).

CHARACTERISTICS OF SENESCENT FIBROBLASTS

In vitro, late-passage fibroblasts adopt an enlarged flattened morphology thought to be indicative of RS (Fig. 2*A*). Fibroblasts derived from the lungs of patients with IPF display the same gross morphology even at early passage (Fig. 2*B*). In contrast, age-matched control fibroblasts of the same passage

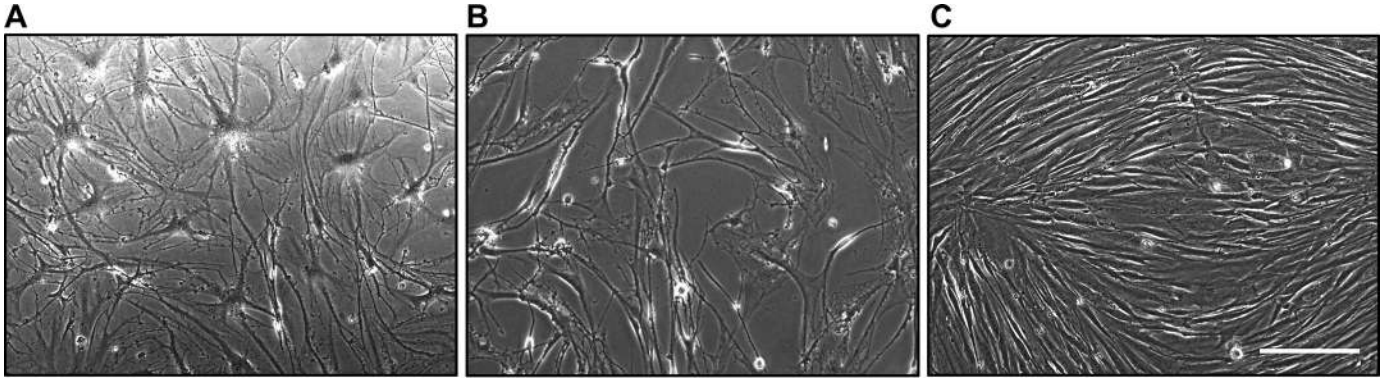

Fig. 2. Morphology of late passage (P8) nonpathological fibroblasts (*A*), early passage (P4) idiopathic pulmonary fibrosis-derived fibroblasts (*B*), and early passage (P1) nonpathological fibroblasts (*C*) is shown. Scale bar = 200 μm.

display a cigar-shaped morphology characteristic of the cell type (115) (Fig. 2*C*). As a result of the increased size of senescent fibroblasts, senescent cultures contain a lower cell density at confluence than younger cultures. The orientation of senescent fibroblasts in culture is characteristically random (Fig. 2, *A* and *B*) compared with the orderly parallel geometry to which early-passage nonpathological fibroblasts conform (Fig. 2*C*). Population-doubling times are also slower in IPF-derived fibroblasts (82, 88).

Within the last few years, several publications have characterized IPF-derived fibroblasts and compared them to age-matched controls. All have concluded that IPF-derived fibroblasts exhibit multiple characteristics of senescence. Telomere length measurements have revealed that telomere attrition is a feature of fibroblasts derived from the lungs of patients with IPF (3). The expression of $p21^{waf1}$ and $p16^{ink4D}$ has been shown to be increased in IPF, in both cultures of explanted fibroblasts (3, 96) and in fibroblasts of histological tissue sections (41, 96). The presence of the SASP has also been confirmed to be a core characteristic of IPF-derived fibroblasts (3, 88, 96). Gene transcripts of proinflammatory and profibrotic SASP factors, IL-6, IL-1β, basic FGF (FGFb), pro-α1-(I) collagen, and TGF-β have all been reported as being significantly increased in IPF lung fibroblasts (3, 88).

FIBROBLAST SENESCENCE: THE GOOD

The influence of senescent fibroblasts in wound repair is an important consideration in regard to IPF pathology because the disease process is thought to result from sequential injuries to the lung (epithelium). Successful wound resolution is crucial for maintaining tissue function and consists of several overlapping phases, the immediate response; the inflammatory response; the proliferation, migration, and contraction phase; and the resolution phase (comprehensively reviewed in Ref. 98). The whole process is orchestrated by resident cells that work in concert releasing cytokines and chemokines that set in motion a series of events that includes cellular migration and the synthesis and deposition of the ECM.

During normal wound healing, the proliferation, migration, and contraction phase marks the point when new granulation tissue is synthesized, facilitating the proliferation of fibroblasts. Within the granulation tissue, local fibroblasts differentiate into α-smooth muscle actin (α-SMA)-expressing fibroblasts, termed myofibroblasts (25, 91). The actin filaments play important roles in many cellular processes, including the generation of contractile force, enabling wound closure.

Studies have shown that senescent myofibroblasts accumulate as part of the normal process of wound healing, at least in animal models. Krizhanovsky et al. (51) examined the accumulation of senescent cells in a murine liver injury model. The senescent cells were identified as myofibroblasts that had initially proliferated in response to the injuring stimulus. Using knockout and transgenic mice, the authors determined that the senescent myofibroblasts present in the injured liver limited the accumulation of fibrotic tissue and facilitated the resolution of fibrosis.

The importance of senescent cells in wound healing has been notably elucidated by Jun and Lau (47), who described how CCN1, a secreted ECM-associated signaling protein, highly expressed at sites of wound repair can induce fibroblast senescence through its cell surface receptors, DNA damage response, and p53 activation, resulting in reactive oxygen species (ROS)-dependent activation of the $p16^{INK4a}$/pRb pathway. The senescent fibroblasts were ultimately identified as myofibroblasts because of an abundance of α-SMA and were shown to accumulate in the granulation tissue of healing wounds, where they expressed antifibrotic genes. Thus, in this model, a worsening of fibrosis occurred in the absence of senescent cells.

Demaria et al. (28) confirmed that senescent fibroblasts were essential for optimal kinetics of granulation tissue formation. In this study, senescent fibroblasts appeared very early in the response to a cutaneous wound, where secreted factors such as PDGF-AA accelerated wound closure by inducing fibroblast-to-myofibroblast differentiation. Whether or not both senescent fibroblasts and senescent myofibroblasts are present at the site of injury is controversial; the distinction may simply be due to some authors identifying α-SMA expression, indicating a myofibroblast phenotype, whereas other groups do not extend their analysis to include identification of myofibroblasts.

Mellone et al. (64) showed that senescent fibroblasts obtained from head and neck and esophageal cancers are predominantly α-SMA positive. Interestingly, the study went on to demonstrate that fibroblasts induced into senescence developed molecular, ultrastructural, and contractile features typical of myofibroblasts. However, RNA sequencing of the two phenotypes revealed significant transcriptomic differences, particularly in genes associated with ECM deposition and organization, essentially suggesting that a senescent fibroblast is a nonfibrogenic, α-SMA-positive myofibroblast.

FIBROBLAST SENESCENCE: THE BAD

The senescent phenotype results in differential gene expression of bioactive mediators, such as inflammatory cytokines, growth factors (13), and ROS (80). The release of such factors by senescent fibroblasts has been shown capable of promoting the proliferation of preneoplastic and neoplastic epithelial cells (52, 78).

In another aging-associated pathology, venous leg ulcers (VLUs), the presence of senescent fibroblasts is thought to be detrimental to wound resolution. VLUs are chronic wounds that within a certain proportion of patients do not resolve successfully and instead persist for months and occasionally years (38). On the basis of clinical findings from VLU wound biopsies (65, 85, 100), it has been suggested that senescent fibroblasts inhibit wound resolution through the secretion of the proteolytic enzymes collagenase, elastase, and stromelysin (38). These ECM-degrading enzymes are particularly problematic for cutaneous wounds, which require sufficient ECM for the migration of cells, such as keratinocytes, to achieve wound resolution.

How the disruptive influence of senescent fibroblasts to cutaneous wound healing translates to IPF pathology is not immediately clear. The thickening of the ECM observed in IPF is likely a result of disturbances between ECM synthesis after injury and then ECM degradation after wound resolution. However, in VLUs, senescent fibroblasts prevent sufficient ECM deposition for wound healing to occur, whereas, in IPF, excessive ECM deposition occurs in the presence of senescent fibroblasts. It is tempting to suggest that senescent fibroblasts resident to areas of fibrosis are not the source of ECM depo-

sition, either directly or through paracrine influence, and are instead attempting to mediate its resolution. Their lack of efficacy in clearing the ECM observed in an IPF lung may be due to the extent that it is deposited after each injuring event.

EPITHELIAL CELL SENESCENCE

Although epithelial cell senescence is outside the remit of this review, its potential to drive the pathogenesis of IPF should also be acknowledged. From histological tissue sections, epithelial senescence is also a well-documented feature of the disease (30, 41, 57, 66, 96), and, in a murine model, their targeted removal through the use of senolytics leads to an attenuation of profibrotic marker expression and increased epithelial cell function (57).

Similar to fibroblasts, senescent epithelial cells are also capable of signaling to other cells within their environment. Thus their profibrotic secretory profile (57, 66) could potentially drive the differentiation of resident lung fibroblasts to myofibroblasts (FMT), ultimately resulting in the excessive collagen deposition that characterizes the disease. Very recently, targeted removal of senescent epithelial cells with senolytic compounds was shown to attenuate SASP mediators and ECM markers, while increasing expression of alveolar epithelial markers ex vivo (57). This study provides the first tantalizing evidence to suggest that senescent epithelial cells contribute to fibrosis. The consequences of epithelial cell senescence might be twofold: *1*) their presence may hinder reepithelialization attributable to their inability to divide, and *2*) their profibrotic secretory profile (57, 66) may drive the differentiation of resident fibroblasts to a synthetic myofibroblast, thereby promoting excessive collagen deposition. However, like fibroblasts, although senescent epithelial cells are a prominent feature in IPF lungs, their influence and role in IPF pathology remain unclear.

Evidence for how cells become senescent in vivo is scant; however, several possibilities exist broadly centered on exposure to stress, termed stress-induced premature senescence (SIPS).

SIPS

Aside from telomere attrition resulting from mitosis, senescence can also be initiated through cellular insult. In vitro SIPS can be induced by a variety of treatment conditions that culminate in DNA damage, including chemical exposure, such as to hydrogen peroxide, irradiation, and ultraviolet light (107). Cells undergoing SIPS adopt a senescent phenotype earlier in mitotic time than RS but still share hallmark features of RS, including cell-cycle arrest and an altered secretory profile.

In vivo the definitive contribution of SIPS to disease pathogenesis is yet to be confirmed. However, several potential hypotheses to its origin have been proposed, including circulating immune cells and mitochondrial abnormalities within the affected cell. Immune-cell-induced senescence was first demonstrated by Braumuller et al. (9), who identified that T-helper-1 cells directly induced permanent growth arrest in cancerous pancreatic β-cells through the release of interferon-γ and tumor necrosis factor-α.

Several major pathways leading to SIPS likely emanate from the mitochondria. Mitochondrial dysfunction has been characterized by increases in mitochondrial mass (56), mitochondrial DNA mutations (112), and increases in ROS (27). Molecular and chemical downregulation of the mitochondrial Rieske iron sulfur protein (RISP), an enzyme located on the inner membrane, has been shown to induce senescence (68), as has the independent inhibition of complexes I, II, and III of the electron transport chain (ETC) (68, 112, 117). Misfiring ETC complexes are thought to result in increased ROS production, ultimately resulting in DSBs to the of the cell through chronic oxidative stress. An imbalance in cellular bioenergetics has also shown to influence the onset of senescence. Decreased ATP and increased AMP-activated protein kinase (AMPK) induce senescence by activating multiple signaling pathways (109).

SENESCENT CELL CLEARANCE

One of the defining features of senescent cells is their abnormal secretory profile, the SASP. The release of a specific array of chemokines and cytokines provides a unique signature, allowing senescent cells to signal to other cells within the local environment. This signaling, among other roles, facilitates their elimination by immune cells, which is arguably the most important function of the SASP, as the persistence of senescent cells is thought to drive age-related pathologies (103, 108) and disease (48, 114).

Senescent cells are cleared by both innate and adaptive immune responses; indeed both monocytes and macrophages are capable of clearing senescent cells (48), as are neutrophils and natural killer (NK) cells (114). Sagiv et al. (95) identified consistently upregulated NK cell ligands on the surface of senescent fibroblasts that promoted NK-mediated cytotoxicity. In addition to soluble factors and cell surface receptors, senescent fibroblasts have also been shown to engage in cell-cell contact, transferring proteins to NK and T cells via cytoplasmic bridges (7). Exocytosis of secretory granules is another method used by senescent cells to signal their NK cell-mediated destruction (94).

The frequency of senescent fibroblasts in the lungs of patients with IPF suggests that the senescent phenotype is inferring a resistance to normal senescent cell clearance. The mechanisms of evasion are presently unknown although possibilities include *1*) immunosenescence, defined as changes to the immune system associated with age, and *2*) a particular subset of senescent fibroblasts avoiding immune surveillance.

STAT3 SIGNALING PATHWAY IN IPF

STAT3 is a member of a family of cytokine-responsive transcription factors and has been identified as being hyperphosphorylated in IPF-derived lung fibroblasts compared with age-matched controls (70, 82). Constitutively activated STAT3 has also been recognized as contributing to the pathology of several cancers (26, 120, 121) and inflammatory diseases (8, 36). As a latent transcription factor, STAT3 is found in the cytoplasm of nonstimulated cells. Following activation, STAT3 translocates to either the nucleus via an importin-α/importin-β1/Ran-mediated mechanism (19) to perform a gene regulatory role or to the mitochondria via GRIM-19 (102), where it associates with complexes of the ETC to facilitate optimal respiration (33, 110).

STAT3 activation is mediated by a number of extracellular stimuli that includes cytokines and growth factors (1). Major

activators of STAT3 are the IL-6 family of cytokines that bind to the IL-6 receptor-α subunit (IL-6Rα) and glycoprotein 130 (gp130) (Fig. 3). IL-6/IL-6Rα binding results in phosphorylation and homodimerization of the signal-transducing receptor gp130. Janus kinase 1 (JAK1) or JAK2 activation follows from gp130 activation. Two JAK molecules of the same class are brought into close proximity, allowing the phosphate groups from gp130 to be transferred across to the newly localized JAKs. Cytoplasmic, nonphosphorylated, STAT3 contains an SH2 domain that facilitates its docking to the phosphorylated tyrosine residues on the JAKs. Once STAT3 is bound to a JAK, it becomes activated via phosphorylation at the tyrosine^{705} residue (pSTAT3^{705}) near the COOH terminus. Serine phosphorylation has also been described at residue-727 (pSTAT3^{727}); however, the serine kinase/kinases involved in activation are not well understood. Once phosphorylated, STAT3 homodimers form and translocate to the nucleus or to the mitochondria. The major negative regulators of STAT3 signaling are the SOCS proteins, in particular SOCS3, which prevent the phosphorylation of STAT3 through direct and indirect interactions with tyrosine kinase SH2 domains (2). A significant reduction in basal SOCS1 mRNA in IPF fibroblasts has previously been reported, as well as a trend toward reduced SOCS3 mRNA (83).

STAT3 TRANSLOCATION TO THE NUCLEUS

In the nucleus STAT3 dimers mediate a transcriptional response of target genes, including *IL-6* and *EGFR*, the anti-apoptotic proteins B cell lymphoma-extra large (Bcl-xL), and Survivin (aka BIRC5), cyclin D1 (CCND1), and other transcription factors such as c-Myc and Twist-related protein 1 (TWIST1) (62, 111). It would appear that phosphorylation is not essential for nuclear translocation, as STAT3 is able to shuttle back and forth from the cytoplasm to the nucleus constitutively via a region located within the coiled-coil domain that is recognized by specific import carrier importin-α3 (60). Phosphorylation is also not absolutely essential for STAT3 to perform a gene-regulatory role; Yang et al. (116) demonstrated that nonphosphorylated STAT3 increased the expression of several genes not upregulated by pSTAT3. Nonphosphorylated STAT3 has been associated with an increased resistance to apoptosis through binding to regulatory regions of proapoptotic genes preventing their expression (105).

STAT3 TRANSLOCATION TO THE MITOCHONDRIA

Although most attention has been centered on its nuclear role, STAT3 also translocates to the mitochondria, where it influences cellular metabolism through facilitating the optimal functioning of the ETC (33, 110). Nonphosphorylated STAT3 and both pSTAT3-Tyr^{705} and pSTAT3-Ser^{727} have been identified in mitochondria (42, 110). Interestingly, only pSTAT3-Tyr^{705} was increased in the mitochondria during recovery from cardiac infarction, suggesting that tyrosine phosphorylation is key to influencing cellular processes in the mitochondria (42).

The mechanism by which STAT3 is transported to the mitochondria is yet to be confirmed, but an association with a component of the ETC, GRIM-19, has been proposed (102). Grim-19 is essential for the successful electron transfer activity of complex I, indicating that STAT3 is also likely to play an integral part in complex I function (44). Supporting this hypothesis, complex I and complex II efficiency is significantly decreased in STAT3-null cells (110). Phosphorylation at either TYR^{705} or Ser^{727} is sufficient for the optimal activities of complex I and II (110). Further support for the association of STAT3 with the inner mitochondria membrane comes from a study by Gough et al. (33), who demonstrated a 50% reduction in cellular ATP levels in STAT3-deficient cells.

Mitochondrial dysfunction is being increasingly recognized as a major contributing factor to aging-associated diseases, including senescence (54). Cells from patients with IPF have been shown to accumulate dysfunctional mitochondria (3, 10, 81), and evidence from animal models suggests that mitochon-

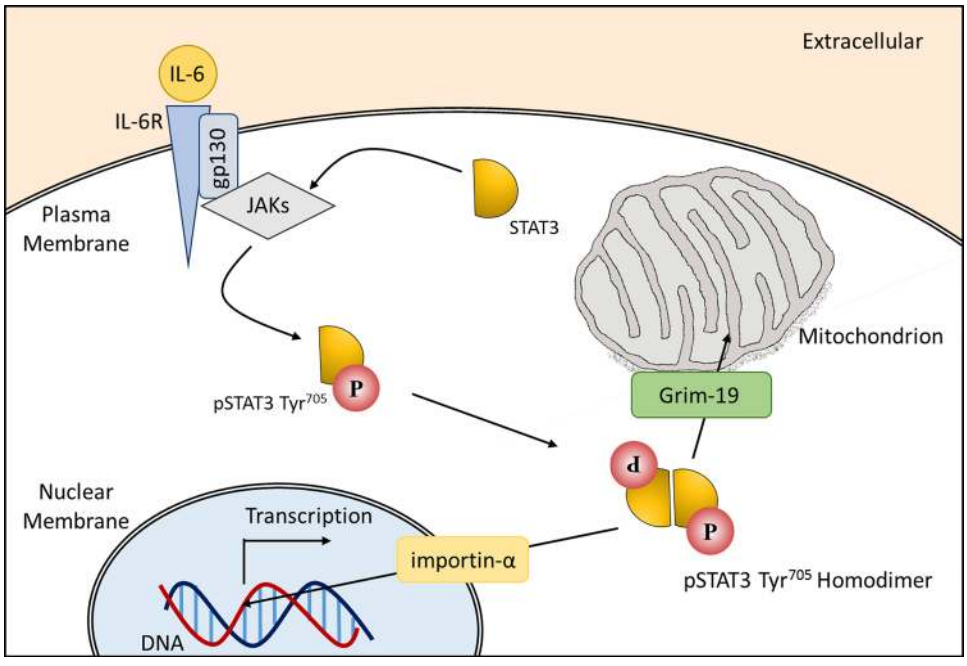

Fig. 3. The Janus kinase 1/signal transducer and activator of transcription 3 (JAK/STAT3) signaling cascade initiated by IL-6 stimulation is shown. Upon IL-6 binding, the signal transduction pathway is initiated by glycoprotein 130 (gp130) followed by JAK activation (not shown); phosphorylated JAKs in turn mediate the recruitment and phosphorylation of STAT3. Phosphorylated STAT3 (pSTAT3) is then released from the receptor, and pSTAT3 homodimers form and translocate to the nucleus via an importin-α/importin-β1/Ran-mediated mechanism or to the mitochondria, where GRIM-19, a component of complex I in the electron transport chain, facilitates STAT3 localization to the inner membrane.

drial dysfunction plays a central role in the pathogenesis of experimental fibrosis (67, 99, 119). Álvarez et al. (3) reported that lung fibroblasts from patients with IPF displayed shorter telomere lengths and simultaneously dysfunctional mitochondria compared with age-matched controls. Reduced mitochondrial function results in a reduction of the critical coenzyme ATP (75). Reduced ATP production has also been identified as a feature of IPF fibroblasts (3), thought to be the result of lower basal respiration.

Mitochondrial dysfunction is unlikely to be the sole mechanism leading to the extent of senescent cells observed in IPF, but it likely plays a part because Correia-Melo et al. (22) showed that senescent fibroblasts depleted of their mitochondria do not develop the characteristic SASP but do undergo cell-cycle arrest.

STAT3 ACTIVITY IN THE SENESCENT PHENOTYPE AND IPF PATHOLOGY

The activation of STAT3 is required for survival and growth of tumor cells (36); therefore, STAT3 is considered an oncogene. As a result, most of what is known about the role of STAT3 in senescence is derived from cancer studies, where the inhibition of the IL-6/STAT3 signaling pathway induces senescence (106, 122).

More recently, the STAT3/senescence axis has been identified as playing a role in the pathologies of wider-ranging diseases. For example, STAT3 activation has been correlated with the development of senescence in a murine model of end-stage renal disease, where inhibition of STAT3 activation resulted in downregulation of genes associated with senescence and the SASP (59). Pharmacological inhibition of the JAK-STAT pathway suppresses the SASP of preadipocytes and endothelial cells as well as SASP-induced adipose tissue inflammation (113). The IL-10/STAT3 signaling cascade has been shown to be a key regulator of the senescent phenotype in macrophages of the eye, and, through its inhibition, normal macrophage function is restored (72). Indirect evidence linking STAT3 to senescence comes from studies by Rodier et al. (92) and Kuilman et al. (53), who revealed that IL-6 is integral to the development of the senescent phenotype through regulating cell-cycle arrest and certain factors of the SASP.

The accumulation of ECM within the lung parenchyma is a pathological feature of IPF, and it appears that STAT3 has a part to play in the transcription of one of the major proteins, collagen I. STAT3 binds to the COL1A2 enhancer and is essential for RNA polymerase recruitment (79).

Oxidative stress is regarded as a contributing factor to the pathogenesis of IPF (reviewed in Ref. 5), and STAT3 has been shown to be a major component of the oxidative stress signaling pathway (14, 74). However, whether STAT3 activation is driving oxidative stress or is merely a result of oxidative stress is yet to be determined.

A STAT3-dependent mechanism has been shown to be capable of inferring fibroblasts with a resistance to apoptosis. Moodley et al. (69) showed that the resistance to induced apoptosis of IPF-derived lung fibroblasts was STAT3 mediated and that IL-6 enhanced Fas ligand (FasL)-induced apoptosis in control fibroblasts but conferred resistance to FasL-induced apoptosis in IPF fibroblasts. The successful resolution of fibrosis necessitates that fibroblast apoptosis occurs at the site of an injury, and these authors (69) implicate STAT3 in the extensive fibrosis observed in IPF through the persistence of apoptosis-resistant fibroblasts, also suggesting that IPF fibroblasts are inherently different from non-IPF fibroblasts.

More recent indirect evidence for a role of STAT3 in promoting fibrosis comes from Yu et al. (119), who identified that aerosolized thyroid hormone therapy significantly resolved lung fibrosis. The thyroid hormone 3,5,3′-triiodothyronine (T3) has previously been shown to significantly reduce STAT3 recruitment to its target promoters in response to IL-6 signaling (20).

It may be that the path to senescence is mediated by more than one pathway or potentially a combination of pathways, converging on several targets, maybe necessary for senescence induction. Cui et al. (24) found that microRNA-34a (miR34a) was capable of inducing senescence, and its expression was increased in the lungs of patients with IPF, particularly in fibroblasts. A causal relationship between mammalian target of rapamycin (mTOR) activation and lung cell senescence has also been identified, as mTOR inhibition has been shown to prevent senescence and inhibit the SASP (43).

At this juncture, there is not enough available evidence. Despite the mounting evidence suggesting STAT3 signaling is important in senescence, whether it drives the onset of senescence or whether it becomes dysregulated as a consequence of senescence (123) remains unknown.

SUMMARY AND FUTURE DIRECTIONS

In nonpathological states, the transient nature of senescent cells allows them to play important roles in cellular processes, such as embryonic development, growth-arresting premalignant cells, and optimal wound resolution. However, the persistence of senescent cells appears to manifest in age-associated diseases such as IPF. Why the onset of the senescent phenotype should normally support tissue homeostasis but drive disease pathology when present in a subset of fibroblasts is unclear. It may be that immune clearance of senescent fibroblasts is compromised as a result of a preexisting pathology or because of a late-onset genetic manifestation in a similar fashion to Huntington's disease (76).

The potential to target senescent cells for removal may be realized with a class of drugs called senolytics, which promote apoptosis in senescent cells through disabling crucial prosurvival pathways (15, 124). However, caution on their use must be raised in light of research highlighting epithelial cell senescence as a pathological feature in IPF (57). Given that end-stage IPF shows ablation of the alveolar epithelium, drugs that indiscriminately target senescent cells may speed up the pathogenesis of an already aggressive disease. In this case, targeting senescent fibroblasts specifically will likely prove a better strategy. A nanoparticle-based targeting approach involving receptor-ligand interaction may prove fruitful, and such therapeutics are presently being tailored toward the epithelium in respiratory diseases such as asthma. However, targeting fibroblasts will be more difficult given the lack of specific markers to unequivocally identify the cell type.

Both RS and SIPS are likely involved in IPF pathology. The incidence of RS cells is an unavoidable consequence of aging (108), and SIPS cells likely accumulate in the lung as a result of tissue-damaging agents. However, whether these cells are

contributing to the excessive fibrosis observed in IPF is yet to be determined. Evidence from animal models suggests that more severe fibrosing occurs in the absence of senescent cells. It remains to be confirmed whether these findings translate into human studies.

In summary, the available literature suggests that senescent fibroblasts are a key aspect of IPF pathology. However, to date, reports linking STAT3 activation and the pathology of IPF are sparse, but studies by O'Donoghue et al. (77) and Pechkovsky et al. (82) indicate that STAT3 dysregulation is a feature of at least a subtype of patients with IPF. Even though evidence for an association is presently lacking, encouragement is drawn from studies linking STAT3 hyperphosphorylation in cancers and also from well-studied roles of STAT3 in nonpathological cellular processes, which ultimately become abnormal during senescence. Future studies should seek to elucidate the molecular mechanisms that lead to the onset of the senescent phenotype, which may help to define whether a factor such as STAT3 can be targeted to rescue the normal phenotype of senescent fibroblasts.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

D.W., K.B., and P.P. prepared figures; D.W., K.B., P.P., J.K.B., M.S., C.G., and D.A.K. drafted manuscript; D.W., J.K.B., S.M., C.P., C.G., and D.A.K. edited and revised manuscript; D.A.K. approved final version of manuscript.

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