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Review

Context-Dependent Roles of p53 in Cellular Senescence and Fibrosis

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ABSTRACT: Cellular senescence is an irreversible growth arrest state and a hallmark of organismal aging. While induction of cellular senescence in healthy organs is undesirable, senescence of specific cell types can be beneficial in certain pathological milieus. For instance, the senescence of activated myofibroblasts helps to limit excessive collagen deposition and preserving tissue homeostasis. Senescent cells express signature gene products, including cell cycle regulators and senescence-associated secretory phenotype (SASP), which includes proinflammatory cytokines, growth factors, and protease inhibitors. Among the senescence regulators, the tumor suppressor p53 plays a pivotal role in suppression of fibrogenesis by dual action: through transcriptional repression of matrix protein genes, and through activation of the cellular senescence pathway in matrix-producing myofibroblasts. Because p53 activation suppresses collagen synthesis, it offers a promising treatment for most fibrotic diseases. However, sustained activation of p53 stress-response in healthy cells may accelerate cellular senescence and aging by promoting the release of SASP. Therefore, the magnitude and timing of p53 activation are critical factors that determine whether its effects are beneficial or detrimental in a given pathological milieu. Here, we discuss the fascinating dual trajectory of p53: its role in driving cellular senescence that contributes to aging, and its capacity to limit the progression of fibrogenesis, a major driver of age-related morbidity and mortality worldwide.

Keywords: p53, Collagens, Fibrosis, TGF-β, Myofibroblasts, Senescence, Epigenetics, Aging

1. Introduction

Cellular senescence, a natural cellular process, is the hallmark of both accelerated and chronological aging of organisms. The cellular proliferation is not infinite, rather cells proliferate for a limited number of cycles before entering permanent growth arrest, a phenomenon called "Hayflick Limit", a cellular state of replicative senescence or cellular aging [1]. However, in response to sustained stresses like reactive oxygen species (ROS)-induced DNA damage, cells can enter a state of irreversible growth arrest known as accelerated senescence. Senescent cells undergo morphological changes and epigenomic reprogramming—including senescence-associated heterochromatin foci (SAHF) formation—and display altered transcriptomics, proteomics and metabolomics profiles. These processes lead to the elevated expression of signature gene products including inflammatory cytokines (e.g., IL-1β, IL-6, TNF-α), growth factors (e.g., TGF-β) and serine protease inhibitors (e.g., PAI-1) collectively called "senescence associated secretory phenotype" (SASP) or "senescence messaging system (SMS) along with SASP regulators (e.g., NF-κB, C/EBPβ, mTOR, p38 MAPK), cell cycle regulators (e.g., p53, p21, p16), and senescence marker SA-β-Gal [2-5]. Chronic SASP secretion from senescent cells may augment senescence in the neighboring healthy cells [6]. Over time, this chronic paracrine propagation of senescence may lead to sustained inflammation, worse fibrosis, organ dysfunction and ultimately organismal aging. However, in

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a context dependent manner, SASP-driven short-term cellular senescence and inflammation are helpful for immune clearance of damaged cells, repair mechanisms and thus beneficial for the organisms. For instance, senescence of cancer cells to prevent abnormal cellular proliferation or induction of senescence in stress-signal-induced myofibroblasts to control excessive matrix protein collagen synthesis [7,8]—the cause of devastating fibrosis in multiple organs that damages the tissue elasticity and organ functions in a variety of pathological milieus. The cell cycle regulator and transcription factor p53 plays a key role in initiation and activation of cellular senescence through functional collaboration with other senescence regulators [4,9]. Interestingly, p53 also plays a significant role in suppression of fibrogenesis—an aging phenotype—in two ways. First, it directly controls transcriptional regulation of matrix protein collagen gene expression [10]; second, it induces cellular senescence in most of the matrix protein collagen producing cells, which significantly lowers overall collagen production.

The p53 protein coding TP53 gene is located at chromosomal locus 17p13.1. The p53 is well known as "Guardian of the Genome," the "Tumor Suppressor," and "Molecule of the Year 1993". The p53 protein was discovered in 1979 as a SV40 T antigen-associated protein by different independent investigators [summarized in 11]. Following its discovery, p53 gained considerable attention because of its role in diverse cellular and molecular processes under physiological and pathological milieus especially in cancers. The chronological advancement of p53 research in different biological processes and biomedical fields has been presented comprehensively by a timeline [12]. The contributions of p53 in DNA damage repair, cellular growth arrest, senescence, metabolism and matrix remodeling are tightly regulated by its posttranslational modifications, such as phosphorylation, sumoylation, and acetylation. These modifications orchestrate its context-dependent interaction with transcription factors, coactivators, corepressors and epigenetic regulators. These specific interactions depend on whether p53 inhibits or stimulates the expression of downstream target genes [13,14]. While transcriptional activation of target genes by p53 is generally results from its direct interaction with cis-regulatory elements—promoter and enhancer, transcriptional repression involves protein-protein interaction between p53, and promoter bound transcription factors/coactivators in the transcriptional initiation complex [Summarized in 10]. For example, the transactivation domain (TAD) of p53 interacts with coactivators such as acetyltransferase p300 (p300) or corepressors like histone deacetylases (HDACs) and modulates target gene expression. The TAD domain also serves as the docking site of its negative regulator murine double minute 2 (MDM2) or human double minute 2 (HDM2), a unique E3 ubiquitin ligase, which is responsible for ubiquitination and proteasomal degradation of p53 protein [15,16]. As TP53 gene is the most frequently mutated gene in the human genome and contributes to a wide variety of cancers (>50% of human cancer) [11,17,18], most of the compounds for cancer therapy have been developed to reactivate p53 by disrupting the p53-MDM2 interaction using MDM2 antagonists. The MDM2 antagonists block E3 ubiquitin ligase-mediated ubiquitination of p53 and its degradation [19-21]. This reactivated p53 suppresses cancer cell growth by inducing cellular senescence and the apoptotic pathway [22]. However, these therapies have not yet succeeded due to the compound's toxic side effects.

Notably, the levels of p53 and its response to stress-signaling decline significantly in specific cell type and tissue of aged mice and humans [23,24]. This decline may explain, at least in part, the causes of less DNA damage repair and the increased incidence of cancer with aging. However, sustained pharmacological activation of p53 and its accumulation in the neighboring healthy cells may be detrimental for cellular and organ function. In this viewpoint, we asked two key questions: First, how does p53 simultaneously contribute to accelerated cellular senescence—a hallmark of aging, and limit the extent of organ fibrogenesis—an aging-associated pathology? Second, is p53 an ideal druggable target for the therapy of aging? The underlying molecular mechanisms by which overexpressed or pharmacologically activated p53 controls these two distinct, but time-dependent overlap biological pathways are discussed [Fig. 1-3].

2. The Tumor Suppressor p53: a Potent Modulator of Profibrogenic Signaling and Multiorgan Fibrogenesis.

In this section, we discuss the critical role of p53 in modulating profibrogenic signal-induced matrix protein collagen synthesis and its broader significance in tissue homeostasis. Fibrosis is a progressive pathological manifestation associated with chronological aging, as well as oxidative stress-, inflammation-, and vascular injury-induced multiorgan diseases in humans. These include Systemic Sclerosis (SSc), Chronic Kidney Disease (CKD), Cirrhosis, Pancreatitis, Peyronie's Disease, Intestinal Fibrosis in Crohn's disease, Idiopathic Pulmonary Fibrosis (IPF), Myocardial Infarction (MI), Atrial Fibrillation (A-Fib) and Heart Failure (HF) [25-37]. An estimated >45% of the disease-related deaths worldwide are linked to tissue fibrosis. Driven by the excessive synthesis and accumulation of extracellular matrix (ECM) proteins, fibrosis causes affected tissues to lose tissue elasticity, which eventually results in organ

failure [38]. In response to oxidative stress, inflammation, and vascular injury, infiltrated mononuclear cells and local fibroblasts secrete transforming growth factor-beta (TGF-β) that triggers the fibroblasts-to-myofibroblast transition (FMT), the major ECM producing cells in the pathogenesis of fibrosis. Notably, TGF-β-induced collagen synthesis during fibrogenesis relies on collaborative efforts of numerous transcriptional activators, repressors, proteases, protease inhibitors, cytokines and kinases [26]. Furthermore, TGF-β induces vascular endothelial cells to undergo endothelial-to-mesenchymal transition (EndMT). The EndMT derived myofibroblast-like cells synthesize matrix proteins and contribute to fibrogenesis [27,33,39]. In response to cellular insult, secreted TGF-β activates serine/threonine kinase TGF-β receptors (TβR1/TβRII) and activated TβRI/II (heterotetramer) phosphorylates the signal transducers Smad2 and Smad3 at the C-terminal SSXS motifs. Phosphorylated Smad2/3 forms a complex with Co-Smad, Smad4, and translocate into the nucleus, where the complex binds to the Smad-binding CAGA element on the collagen gene promoter. The acetyltransferase p300 (p300) interacts with pSmad2/3/Smad4 complex on the collagen gene promoter, and this protein-protein interaction is essential for TGF-β-induced stimulation of Type I collagen synthesis in myofibroblasts. Disruption of the physical and functional interaction of pSmad with p300 or pharmacological inhibition of acetyltransferase activity of p300 leads to suppression of TGF-β-induced collagen synthesis and fibrogenesis [40-43], identifying the Smad-p300 interaction interface as a promising therapeutic target to attenuate fibrogenic signaling.

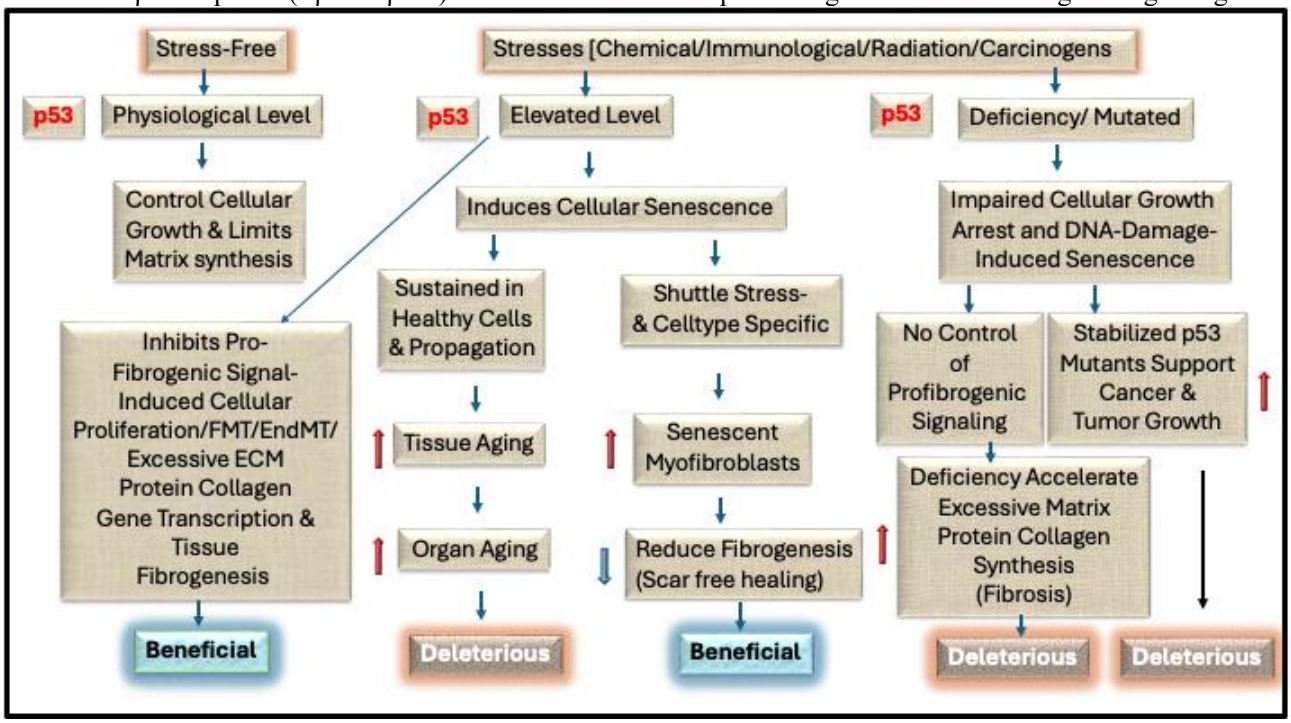

Figure 1. Schematic illustrations showing the involvement of p53 in cell physiology and cell pathology. Under stress-free milieu, physiological level of wildtype p53 regulates the expression of genes controlling cellular growth and limits matrix protein synthesis. Stress-induced p53 may be beneficial or detrimental for cellular function. The elevated p53 limits the profibrogenic signal-induced cellular proliferation, differentiation and fibrogenesis (**Left panel**); short-term overexpression of p53 is associated induction of cell-type specific senescence including matrix producing myofibroblasts and reduction of tissue fibrogenesis (**Middle panel**). Sustained activation of p53 in the healthy cells is detrimental due to cellular senescence or even apoptosis and aging (**Middle panel**). The deficiency or mutation of p53 (with a few exceptions) is associated with detrimental abnormal cellular growth, tumor formation and worse fibrosis (**Right panel**).

Several studies have established the cell cycle regulator p53 as a critical modulator of extracellular matrix proteins (ECM), matrix metalloproteinase (MMP), tissue inhibitor of matrix metalloproteinase (TIMP) and plasminogen activation system including serine proteases plasminogen activators (t-PA/uPA) and their inhibitor, PAI-1 [44-47]. Thus, p53 plays a pivotal role in maintaining tissue homeostasis. Subsequently, the molecular mechanisms underlying p53-mediated transcriptional regulation of TGF-β-induced Type I collagen gene expression have been extensively investigated in human skin fibroblasts [10]. This study demonstrated that although p53 overexpression increased basal and TGF-β-induced PAI-1 expression—a potent inhibitor of serine proteases (t-PA/uPA) and regulator of cellular senescence—TGF-β-induced collagen gene

transcription was significantly suppressed in dermal fibroblasts. Notably, Type I collagen gene expression was significantly elevated in p53 null murine embryonic fibroblasts relative to wildtype controls in the absence and presence of TGF-β. This indicates that cellular p53 modulates both physiological and profibrogenic signal-induced matrix protein synthesis, thereby contributing to tissue homeostasis [10]. Consistent with these findings, basal p53 expression is markedly reduced in fibrotic lung fibroblasts (fLfs), which correlates with elevated collagen synthesis. Furthermore, while transduction of fLfs with p53-expressing adenovirus reduces the expression of matrix proteins, lentiviral shRNA-mediated silencing of baseline p53 in normal lung fibroblasts leads to elevated expression of profibrogenic genes [48]. These findings corroborate previous research on p53-mediated regulation of collagen synthesis in human dermal fibroblasts and p53 null mouse embryonic fibroblasts [10]. Furthermore, adenovirus-driven overexpressed p53 significantly inhibits the expression of α-SMA and collagen in hypertrophic scar fibroblasts (HSFs) compared to normal dermal fibroblasts. This inhibition is driven by HSF autophagy and apoptosis [49]. Using a rabbit ear scarring model, this study further demonstrates that wildtype p53 overexpression in scar tissue leads to reduced collagen fiber deposition and smaller scar formation [49]. Together, these findings establish that p53 acts as a negative regulator of profibrogenic signal-induced matrix protein synthesis, and the physiological level of p53 is required to modulate the profibrogenic signaling in skin and lungs fibroblasts to maintain tissue homeostasis (Fig. 1 and Table 1).

Table 1. The roles of p53 in different cell types to control profibrogenic matrix synthesis as well as cellular senescence, the hallmark of aging.

Cell Types	p53 Wildtype/Specific Mutants	Method of Manipulation to Increase p53 Activity	p53 KO/Deficiency /Specific Mutants/Inhibitor	Method of Manipulation to Deplete p53 Activity	Endpoint Readout	Biological Effects of p53	Refs.
Dermal Fibroblasts	Matrix Protein Down	Overexpressed/ Etoposide	Matrix Protein Up	Genetic KO/Mutants	Collagen I, PAI-1	Anti-Fibrotic	[10]
Hypertrophic Scar Fibroblasts	Matrix Protein Down	Adeno-overexpressed	Matrix Protein Unchanged	ShRNA	α-SMA, Collagen I, III	Anti-Fibrotic	[49]
Normal Lung Fibroblasts	Matrix Protein Down	Base line level	Matrix Protein Up	Lentivirus p53 ShRNA	Collagen I, α-SMA, Fibronectin	Anti-Fibrotic	[48]
Fibrotic Lung Fibroblasts	Matrix Protein Down	Adeno-overexpressed	Matrix protein Up	Pathology-induced	Collagen I	Antifibrotic	[48]
Cardiac Fibroblasts	Matrix Protein Down	Overexpressed /AIRN	Matrix Protein Up	MiR-125b/Gene KO	Type I Collagen	Anti-Fibrotic	[52, 53]
Hepatic Stellate Cells	Matrix Protein Down	IL-10/IL-22/ Nutlin3a	Matrix Protein Up	PFT-α	α-SMA, Collagen	Anti-Fibrotic	[77, 79]
Pancreatic Stellate Cells	Matrix Protein Down	Nutlin-3a (RG7112)	Matrix Protein Up	Pancreatic cancer	α-SMA, Collagen, Elastin	Anti-fibrotic	[51]
Podocytes	Matrix Protein Up	Alport Syndrome	Matrix Protein Worse	Pod-Specific KO	Collagen	Anti-fibrotic	[64]
Murine Cardiac Fibroblast	Matrix Protein Down	Airn	Matrix Protein Up	SiRNA	α-SMA, Collagen	Anti-Fibrotic	[82]
Murine Cardiac Fibroblasts	Matrix Protein Down	CX-5461	Matrix Protein Up	PFT-α, Lentivirus p53 ShRNA	Collagen I, III, α-SMA, PAI-1	Anti-Fibrotic	[83]
Human Cardiac Fibroblasts	Matrix Protein Down	Rhein	Matrix Protein Up	Hypoxia	Collagen, α-SMA	Anti-Fibrotic	[85]
Neonatal Rat Cardiac Fibroblasts	Matrix Protein down	Tetramisole, Leonurine	Matrix Protein Up	PFT-α	Collagen, α-SMA	Anti-fibrotic	[]65, 81]
Mice and Rats Proximal Tubular epithelial cells	Matrix Protein Up	Ischemic Renal Injury (IRI)-induced	Matrix Protein Down	PTC-specific KO/ siRNA	Collagen, α-SMA, pSmad	Pro-fibrotic (*Exceptional*)	[60, 61]
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Mouse Embryonic Fibroblasts	Senescence Up	High Passage-induced	Senescence Down	p53 Knock-Down	Morphology, SA-β-Gal	Pro-senescent	[68]
A-549 Cells	Senescence Up	Bleomycin	Senescence Down	PAI-1 inhibition (Indirect)	SA-β-Gal, PAI-1, p53, p21, IL-6	Pro-senescent	[70]
Atrial Fibroblasts	Senescence Up	High Passage-Induced	Senescence Down	RNAi /shRNA	p21, PAI-1	Pro-senescent	[55, 56]
Neonatal Murine CF	Senescence Up	Hypoxia/Reoxygenation	Senescence Down	SiRNA	SA-β-Gal, p16, p21	Pro-senescent	[76]

Rat Ventricular Myocytes	Senescence Up	Doxorubicin	Senescence Down	PFT-α	SA-β-Gal, p53	Pro-senescent	[88]
Human Coronary Artery Endothelial Cells	Senescence Up	Homocysteine	Senescence Down	PAI-1 inhibition (Indirect)	SA-β-Gal, p53, PAI-1, p16	Pro-senescent	[66]
EA.hy-926 Endothelial Cells	Senescence Up	Doxorubicin/Homocysteine	Senescence Down	PAI-1 Inhibition (Indirect)	SA-β-Gal, p53, PAI-1, p16, p21	Pro-senescent	[9,66]
Rat and Mouse Hepatic Stellate Cells (HSCs)	Senescence Up	IL-10/IL-22	Senescence Down	Serum Free, PFT-α	SA-β-Gal, p21, Stat3, Socs3,p53	Pro-senescent	[77, 79]
Human BJ Dermal Fibroblasts	Senescence Up	Cyr61/CCN1	Senescence Down	Lentivirus ShRNA	SA-β-Gal, p16, p53, Rb, IL-6, IL-1b, Proliferation	Pro-senescent	[7]

The antifibrotic nature of cellular p53 is further documented by the observations that etoposide, an inducer of p53 expression, represses TGF-β-induced collagen synthesis in human dermal fibroblasts [10]. This article originally shows that overexpressed p53 inhibits Smad-dependent TGF-β responses and collagen gene expression without affecting Smad expression or its phosphorylation or its complex formation with Smad4 and translocation of Smad2/3/4 from cytoplasm to nucleus. Mechanistically, p53 physically interacts with p300 sequestering it away from the TGF-β-stimulated pSmad2/3 transcriptional complex on the collagen gene promoter that leads to suppression of TGF-β-induced collagen synthesis. Overexpression of p300 completely reverses the p53-mediated suppression of TGF-β-induced collagen gene transcription in dermal fibroblasts even in the presence of excess p53. Notably, like overexpressed wildtype p53, three tumor-derived p53 mutants (p53-175, p53-248, p53-273) also inhibit TGF-β-induced collagen gene transcription. However, two mutants derived from rheumatoid synovium (p53-213 and p53-239) are unable to block the TGF-β-induced collagen gene transcription. Instead, these mutants further stimulate collagen gene transcription by 20-30%, indicating they act as dominant negative mutants and suppress endogenous wildtype p53 protein activity [10]. Similarly, the human pancreatic ductal adenocarcinoma (PDAC) tumors with p53 missense mutations also exhibit higher expression of fibrosis-associated genes than wildtype and p53 null tumors. This worse fibrosis is driven by the inhibition of macrophage infiltration and reduced clearance of cancer cells [50]. Whether these synovium or PDAC-derived mutants lose their capacity to interact with p300 remains a critical question for future investigation. Notably, Nutlin-3a (10 μM)-mediated activation of wildtype p53 in cancer-associated pancreatic stellate cells (PSCs) decreases the expression of ECM proteins including collagen and elastin [51]. Similarly, activation of wildtype p53 in mouse pancreatic stellate cells (PSCs) resulted in decreased expression of profibrogenic α-SMA and collagen gene expression. Furthermore, treatment of tumor-bearing mice with RG7112 (200 mg/kg), a clinical form of Nutlin-3a and a more potent activator of p53, led to decreased levels of pancreatic fibrosis [51]. Together, these results further establish that p53 is a potent and selective endogenous transcriptional repressor of inflammatory and profibrogenic signal-driven increased collagen gene expression and fibrogenesis (Fig. 2 left; Table 1). Because p53 activates key senescence regulators like p21 and PAI-1, we cannot rule out the contribution of the p53-p21-PAI-1 axis in driving senescence in myofibroblasts and decreased synthesis of matrix protein collagens, alongside direct transcriptional suppression, as supported by other studies [52, 53]. Therefore, p53 activation is beneficial in activating myofibroblasts under chronic fibrogenic signaling.

It is important to note that the epigenetic regulator p300 promotes the formation of super-enhancers at non-coding genomic elements, driving senescence-associated gene expression and chronic inflammation. Consistent with this, shRNA-mediated reduction of the p300 decreases SA-β-Gal staining and suppresses cellular senescence process [54]. Recent evidence highlights the p300-p53 axis as a central driver of the atrial pro-fibrotic environment. Levels of p300 are significantly elevated in the left atrial tissues derived from patients with Atrial Fibrillation (A-fib), aged mice, and aged atrial fibroblasts. This upregulation of p300 is associated with increased expression of senescence regulators p53 and its downstream targets p21 and PAI-1. Mechanistically, this pathway operates in a p53-dependent manner, as studies demonstrate that siRNA-mediated p53 knockdown reduces the expression of downstream targets like p21 [55,56]. While pharmacological inhibition or RNAi-mediated knockdown of p300 in aged human atrial fibroblasts reduces the expression of senescence marker SA-β-Gal, as well as the senescence regulators PAI-1 and p21, RNAi-mediated knockdown of p53 is also associated with decreased expression of PAI-1 and p21 [56]. Collectively, these results establish the p53-p300 complex as a central regulatory hub for atrial fibroblast senescence. Based on the timelines required for p53-mediated significant transcriptional repression of collagen synthesis (48 h) (10) and the completion of senescence process *in*

vitro (>5 days) (9), we propose a hypothetical model where p53 exerts dual-regulatory roles. As an early effect, p53 disrupts transcriptional complexes on the collagen gene promoter to suppress matrix protein synthesis. Concurrently or subsequently, the sequestered p300-p53 complex may activate other senescence regulators to drive cellular senescence process as a late effect (Fig. 2, right) in a cell- and stressor-dependent manner.

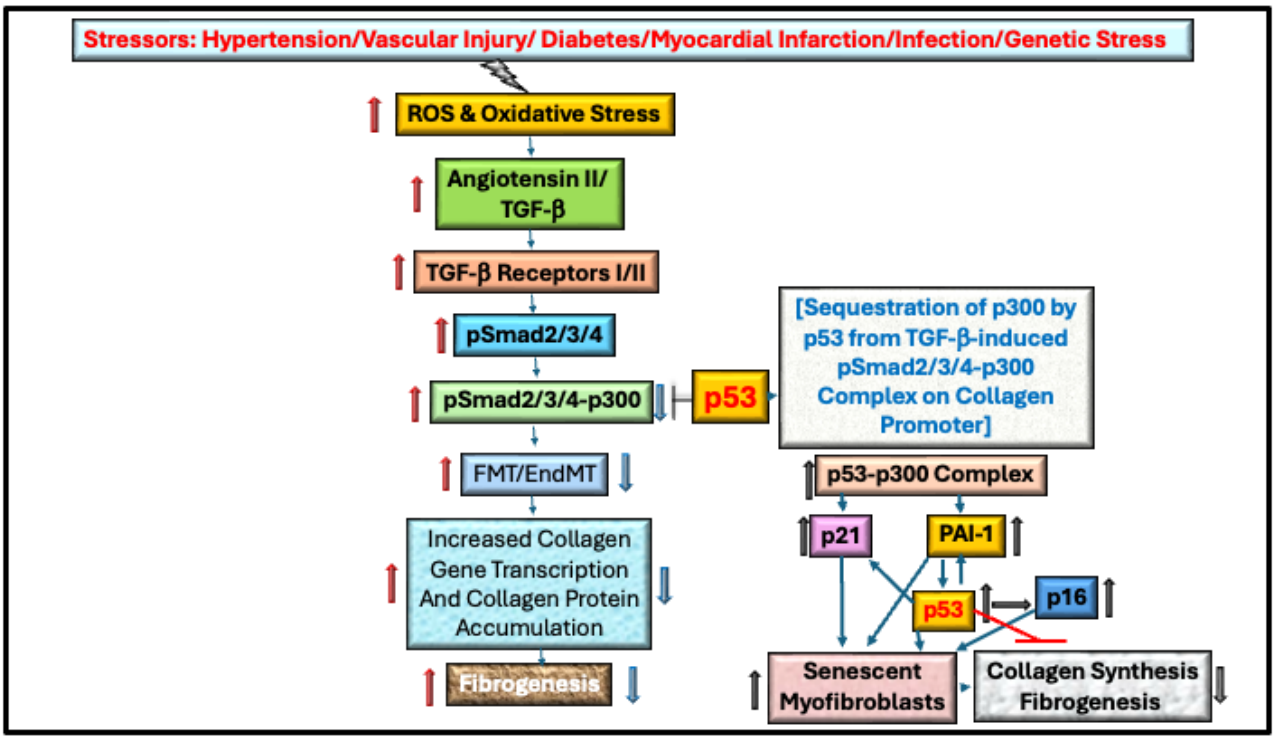

Figure 2. Schematic Illustration Showing the Anti-fibrotic Pathways of p53. Stressors-induced oxidative stress increases the levels of pleiotropic cytokine TGF-β and downstream profibrogenic signaling. Upon binding TGF-β, activated TGF-β receptors (TβR I/II) serine/threonine kinase phosphorylates receptor Smad2/3 at the C-terminal SSXS motif. pSmad2/3 heterodimerize with Co-Smad, Smad4 and translocate to nucleus and bind to the CAGA DNA element on collagen gene promoter. Coactivator acetyltransferase p300 interacts with Smad complex and stimulates target gene expression. The physical and functional interaction of pSmad2/3 with p300 is essential for TGF-β-induced collagen synthesis. Overexpressed p53 can mediate direct transcriptional inhibition through sequestration of p300 from profibrogenic signal-induced pSmad2/3/4-p300 complex on collagen gene promoter (**Left panel**); and via induction of myofibroblast senescence through p53-p300 mediated activation of p21-PAI-1-p16 senescence regulatory-network and suppression of collagen synthesis. The positive feedback loop in p53- p21-PAI-1-p16 axis contributes to cellular senescence as described in the text (**Right panel**).

Beyond its role in age-related atrial fibrillation, the p300/p53 axis acts as a key regulator of the Endothelial-to-Mesenchymal Transition (EndMT). While EndMT-derived myofibroblast-like cells are essential for embryonic organ development [57,58], stress-induced EndMT-derived myofibroblast-like cells contribute to adult organ fibrosis [59]. The antifibrotic function of p53 in TGF-β-induced EndMT is supported by altered expression of numerous miRNAs in EndMT-derived myofibroblasts compared to normal endothelial cells [39]. Specifically, miR-125b—which is dysregulated in various cardiovascular diseases. Interestingly, protein level of cellular p53—a target of miRNA-125b—is downregulated in profibrogenic signal-induced EndMT-derived myofibroblast-like cells [39] indicating collagen producing EndMT-derived myofibroblasts like cells are significantly free of anti-fibrotic p53. Subsequent studies demonstrated that overexpressed miR-125b downregulates the p53 protein *in vitro* and *in vivo* that plays a significant role in profibrogenic signal-induced cardiac fibroblast-to-myofibroblast transition (FMT) and accelerated cardiac fibrogenesis [52]. These findings indicate that downregulation of p53—a transcriptional repressor of collagen—is one of the major causes of miR-125b-induced EndMT and FMT and elevated matrix protein synthesis. Therefore, pharmacologically restoring p53 may be an ideal therapeutic approach to inhibit profibrogenic signaling and cardiac fibrogenesis [10,39,52]. However, this inference is not applicable in a rare pathological milieu. Molitoris and colleagues [60] demonstrated that administering p53-siRNA (12mg/kg iv injection 4 h after IRI) reduces ischemic renal injury (IRI)-induced overexpression of p53 in the proximal tubule cells (PTCs) and ameliorates IRI and cellular

apoptosis in a rat model [60]. Similarly, PTCs-specific deletion of p53 in a murine model of IRI prevents IRI-induced renal interstitial fibrogenesis, as evidenced by reduced collagen deposition on day 16, ultimately preserving renal structure and function. Mechanistically, the absence of p53 in proximal tubular epithelial cells prevents renal tissue damage by mitigating IRI-induced oxidative stress, inflammation and apoptosis [61]. Therefore, p53 activation in proximal tubular epithelial cells is likely to be harmful in response to acute renal injury. In contrast to the renal protection observed in proximal tubule-specific p53 knockout mice, global p53 deletion or pharmacological inhibition of p53 with PFT-α (2.5mg/kg/daily ip for 3 or 7 days) in mice develops worse renal injury in response to IRI as evidenced by increased inflammation, tubular cell apoptosis and the deposition of matrix proteins including collagen and fibronectin [62]. Similarly, pharmacological inhibition of p53 with pifithrin-a (PFT-α) (3mg/kg daily ip for 2 days or 7 days) exacerbates renal fibrosis in rats following IRI [63]. In an animal model of Alport Syndrome, an inherited human kidney disease, global p53 deficiency causes worse renal inflammation, glomerular injury and renal fibrosis, ultimately impairing renal function [64]. Furthermore, podocyte-specific deletion of p53 in 15-week-old Alport syndrome mice worsened renal fibrosis, glomerular injury, and renal dysfunction compared with wild-type p53 expressing Alport syndrome mice [64]. These results provide strong evidence that p53 is antifibrotic and protects the kidneys from injury-associated pathologies with the rare exception of rodents with PTC-specific p53 deficiency. The involvement of p53 in myocardial infarction (MI)-associated reparative cardiac fibrosis has been further documented in both rat model of MI and human patients. Gao and colleagues [65] demonstrated that tissue nonspecific alkaline phosphatase (TNAP), an enzyme that hydrolyzes pyrophosphate to phosphate involved in vascular mineralization and calcification, is upregulated in serum and myocardial tissues derived from patients with MI. TNAP is also significantly upregulated in rat model of MI and associated with increased TGF-β1 level, myofibroblast differentiation and elevated collagen synthesis. Notably, pharmacological inhibition of TNAP with tetramisole (11 mg/kg/day ip 7 days before MI), an imidazothiazole-derivative, ameliorates ventricular fibrosis (>50% inhibition) and improves cardiac output as evidenced by increased ejection fraction and fractional shortening etc. In primary cultures of neonatal rat cardiac fibroblasts, TNAP inhibition with tetramisole (1mM for 24-48h), significantly attenuates hypoxia-induced myofibroblast differentiation and ECM protein gene expression by upregulating the p53 and p21 axis and suppressing Smad-dependent TGF-β responses. Furthermore, the p53 inhibitor, PFT-α or p53 siRNA abrogates this protective effect of tetramisole, indicating the antifibrotic action of the TNAP inhibitor is mediated, at least in part, by the activation of the p53 signaling axis [65] (Table 1).

These observations align with the established paradigm that p53 exerts its antifibrotic effects by disrupting the TGF-β-induced Smad-p300 signaling pathway [10]. Collectively, these findings support a dual-action therapeutic strategy: pharmacological activation of p53 to both disrupt the profibrogenic transcription initiation complex on the collagen gene promoter and induce myofibroblast senescence, offering a robust approach to combat multi-organ fibrosis.

3. p53:a Key Determinant of Cellular Senescence and the Severity of Fibrosis.

The role of p53 as a master regulator of cellular senescence is highly context dependent. It can act as either a driver of systemic aging or a critical physiological brake on tissue fibrosis. In this section, we discuss how p53 directs the induction of cellular senescence across different cell types exposed to different stressors. Under conditions of acute stresses—such as exposure to low dose of anticancer drug doxorubicin (50 nM for 4 days) [9] or elevated homocysteine (Hcy) (750 μM for 4-5 days), a known risk factor of cardiovascular diseases [66]—p53 levels are significantly upregulated across diverse cell types. This induction of premature senescence is evidenced by robust SA-β-Gal staining, a bona fide senescence marker, and activation of key senescence regulators, including p53, PAI-1, p21 and p16. Notably, pharmacological inhibition of cellular PAI-1, a SASP, protects against doxorubicin- and Hcy-induced accelerated cellular senescence. This protection is achieved through suppression of PAI-1 activity and downregulation of senescence regulators including p53, p21 and p16 [9, 66]. An obvious question is how PAI-1-specific small molecule inhibitor, TM5441 (10 μM) blocks not only the senescence igniter-induced PAI-1 activity but also other senescence regulators like p53, p21 and p16. One possibility is that doxorubicin [9] or homocysteine [66] triggers cellular senescence through generation of oxidative stress, induction of DNA damage response and activation of p53 pathway. Activated p53 induces the expression of its direct downstream targets PAI-1 and p21 [9, 67, 68]. p53 can indirectly induce p16 expression, by stabilizing Lamin A/C. In turn, stabilized LaminA/C reduces the level of epigenetic regulator polycomb repressive complex-1 (PRC1), a repressor of p16 promoter, and its reduction is associated with increased expression of p16 [69]. While bleomycin-mediated overexpressed PAI-1 increases p53 protein levels by suppressing p53 degradation and increases SA-

β-Gal positive A549 cells (>50%), pharmacological or genetic inhibition of PAI-1 leads to recovery of proteasomal degradation of p53 and decreased SA-β-Gal positive cells to control levels [70]. Because this supportive evidence derives from epithelial and cancer cells, these observations may not apply to fibroblasts or other normal cell types. Nevertheless, these reports establish a positive feedback loop within p53-p21-PAI-1-p16 axis where elevated p53 induces the expression of PAI-1, p21 and p16. In turn, elevated PAI-1 stabilizes the p53 protein, a direct activator of downstream senescence regulators and thus sustained activation of this loop may trigger irreversible growth arrest or cellular senescence (see Fig. 2 right). Another valid explanation is that stressor-ignited Nox2 or Nox4 increases the levels of specific senescence regulators like PAI-1 [71,72]. This, in turn, may augment NOX2/4 levels and further increases the levels of ROS production, indicating suppression of PAI-1 reduces ROS levels and downstream other senescence regulators such as p53, p21 and p16 [9]. Thus, PAI-1 inhibitors like TM5441 suppress doxorubicin- or homocysteine-induced cellular senescence may be not only by directly inhibiting PAI-1 activity, but also by activating Nrf2—an activator of major antioxidant genes— and by inhibiting the NOXs-ROS axis and downstream senescence regulators, including p53-p21-p16 axis [9,66] (Table 1).

The significance of p53 in cellular senescence and aging is further documented by an accelerated aging study in a nematode [73], where p53 plays a pivotal role in mediating the anti-aging effects of JM10001(200mg/L for 10 days), a natural product that extends both lifespan and healthspan of *Caenorhabditis elegans*. Furthermore, this plant-derived compound JM10001 (1-2 g/kg daily from day 16 to day 37) alleviates aging pathologies in doxorubicin (5mg/kg, ip on day 0 and day 10)-induced accelerated aging mice. This effect is achieved by reducing the doxorubicin-induced increased expression of p53 in kidney and liver. These findings indicate further that p53 is a key regulator in driving cellular senescence process and aging, operating through multiple pathways such as activation of p21 or PAI-1, cellular growth arrest and induction of premature cellular senescence [73]. These results clearly demonstrate that p53 is a promising drug target for controlling cellular senescence, delaying accelerated aging, and extending lifespan.

The central question is how p53 governs two apparently opposing biological processes: detrimental cellular aging and protective anti-fibrogenesis. As noted, cellular senescence is highly context-dependent, it can be detrimental when it propagates systemic aging yet serving a protective role by limiting aberrant tissue remodeling. Numerous studies identify premature senescence as a key regulatory mechanism in controlling tissue fibrosis. For example, in transverse aortic constriction (TAC)-induced left-sided heart failure model, the levels of senescence marker SA-β-Gal and senescence regulators p53, p16, p21 and PAI-1 are significantly elevated in perivascular fibrotic areas compared to sham-operated controls [74]. This study identified myofibroblasts as the predominant senescent cells in the TAC operated hearts. Interestingly, inhibiting the senescence process by genetic deletion of both p53 and p16 in mice, led to worse cardiac fibrosis and a severe decline in cardiac output in TAC-operated mice compared to wildtype TAC controls [74]. These findings highlight the perivascular bed as a hotspot for cardiovascular aging [75] and reinforce the concept that p53 limits the extent of fibrogenesis by directly suppressing collagen gene transcription and inducing myofibroblast senescence in the failing hearts. Furthermore, cardiac-specific overexpression of CCN1 (CYR61) in this model, an inducer of p53 and fibroblast senescence [7], reduced perivascular fibrosis by 50% and improved cardiac structure and function compared to dominant-negative CCN1 expressing mice [74]. Collectively, these data establish that myofibroblast senescence as an essential anti-fibrotic mechanism, marking a shift from matrix protein collagen producing to matrix metalloproteinase (MMPs)-producing cells. Consequently, this pathway represents a potential therapeutic target for controlling myocardial fibrosis associated with cardiac hypertrophy and heart failure. Mechanistically, CCN1/Cyr61 induces this cellular/myofibroblast senescence through the activation of the p53-p16-RB pathways [7]. The anti-fibrotic capacity of p53 is further elucidated by its regulation of fibroblast proliferation and matrix protein synthesis. In response to TAC, fibroblast-specific deletion of p53 results in a massive accumulation of Tcf21-lineage cells that is correlated with the altered p53-mediated gene expression and worse cardiac fibrosis compared to wild type TAC mice [53]. By day 14 of TAC, there is a 15-fold increase in Ki67-positive fibroblasts and perivascular fibrosis in fibroblast-specific p53KO hearts compared to TAC-operated wildtype hearts. However, by day 28, proliferation of p53KO cardiac fibroblasts significantly drops accompanied by worse interstitial cardiac fibrosis. Together, these findings demonstrate how cardiac fibroblast proliferation and ECM synthesis are synchronized in part by p53 that controls the timing and extent of fibrosis in the murine model of left ventricular pressure overload [53]. Therefore, the results obtained in p53 deficient embryonic fibroblasts and miR-125b-mediated downregulation of p53 in EndMT- and FMT-derived myofibroblasts [10,39,52] further explain that the increased level of fibrosis is driven by a lack of p53-mediated transcriptional repression of matrix protein genes, cell-cycle arrest, and myofibroblast senescence.

This has been supported by the observation that while overexpressed p53 inhibits fibroblast proliferation, miR-125b-mediated downregulation of p53 reverses human cardiac fibroblast growth arrest [52].

Consistently, Angiotensin II failed to induce cellular proliferation in the anti-miR-125b-LNA-treated murine hearts confirming p53 plays a significant role in miR-125b-mediated profibrogenic responses [52]. Furthermore, p53 deficiency in the left coronary artery ligation-induced ischemic myocardium is associated with >60% decrease in SA-β-Gal positive senescent fibroblasts and >60% increase in matrix protein collagen deposition by day 7 compared to controls [76]. Together, these findings establish that pharmacological activation of p53 is a compelling strategy to combat multiorgan fibrosis by repressing collagen gene transcription and subsequent triggering myofibroblast senescence [Fig. 2].

4. Is Pharmacological Modulation of p53 Activity a Viable Approach to Control Fibrogenesis and Cellular Senescence?

Multiple preclinical studies on anti-fibrotic therapy reveal the significant involvement of p53 in controlling fibrogenesis and cellular senescence. For instance, attenuation of the carbon tetrachloride (CCL_4)- and porcine serum-induced rat liver fibrosis by IL-10 is primarily linked to the senescence of activated hepatic stellate cells (HSCs), the major producers of ECM proteins in the liver. Mechanistically, IL-10 (20ng/ml for 24h) triggers the senescence of HSCs through activation of Stat3-dependent cell cycle arrest and increased expression of senescence regulators p53 and downstream p21 [**77**]. More significantly, treatment with Pifithrin-α, (20 μM for 24 h) a specific inhibitor of p53, abrogates IL-10-induced increased expression of senescence regulators in activated HSCs and stimulates collagen gene expression. These results indicate that IL-10-induced premature senescence of activated HSCs and the attenuation of liver fibrosis are mediated through the activation of the p53 pathway [77]. Consistent with this, IL-10 knockout mice develop exacerbated cardiac fibrosis and impaired cardiac output compared to wildtype mice following Isoproterenol (45 mg/kg/day for 14 days) administration and TAC-induced left ventricular pressure overload. Conversely, recombinant IL-10 (50mg/kg) infusion attenuates Isoproterenol-induced cardiac fibrosis by activating Stat3 and concurrently inhibiting the pro-inflammatory NF-kB pathway [78] further indicating IL-10-induced Stat3-p53 axis may serve as a protective, antifibrotic role in these mouse models of cardiac fibrosis. Similarly, IL-22 exhibits antifibrotic properties and accelerates the resolution of liver repair by activating Stat3. Overexpression of IL-22 promotes senescence in murine HSC, as evidenced by increased SA-β-Gal staining, upregulation of p53, downstream p21 expression, and decreased expression of myofibroblast marker α-SMA in fibrotic livers and cultured HSCs. These findings indicate that IL-22 exerts it antifibrotic effects through activation of Stat3-p53-p21 axis-mediated senescence in HSCs [79]. Hence, these studies further emphasize that p53-driven HSC senescence is critical for amelioration of liver fibrosis [80]. The viability of p53 as a drug target for fibrosis therapy is further supported by the therapeutic effects of Leonurine (LE), a pseudoalkaloid plant product with anti-inflammatory and antioxidant properties. LE (10-40 μM) significantly inhibits Angiotensin II (1 μM)-induced cardiac profibrogenic responses, including FMT and collagen synthesis, thereby alleviating the progression of myocardial fibrosis. Interestingly, LE stimulates p53 expression and its antifibrotic effect is blocked when p53 is inhibited using PFT-α (30 μM). These findings indicate that LE-induced p53 plays a dual role in mediating its antifibrotic effects by inducing the myofibroblast senescence pathway [81], and by direct inhibition of profibrogenic signal-induced collagen gene transcription [10], supporting p53 as a potential drug target to control stress-induced multiorgan fibrogenesis. p53 is also implicated in antifibrotic action of Airn, a lncRNA, that is downregulated in diabetic hearts and high glucose-treated cardiac fibroblasts [82]. Notably, the Airn knockdown mice spontaneously develop cardiac fibrosis affirming the intrinsic antifibrotic nature of Airn. Importantly, overexpressed Airn blunts diabetes-induced cardiac fibrosis in a murine model of diabetic cardiomyopathy (DCM) and high glucose-induced fibroblast growth, FMT and matrix protein collagen synthesis. Mechanistically, Airn exerts its antifibrotic activity by stabilizing insulin like growth factor mRNA-binding protein 2 (IMP2), which in turn stabilizes p53 mRNA and upregulates p53 protein levels. Furthermore, siRNA-mediated silencing of p53 blunts these protective effects of Airn, highlighting p53 as a promising therapeutic target in managing DCM-associated cardiac fibrosis [82] (Table 1). It is apparent that Airn-mediated p53 induction and fibroblast growth arrest induces cellular senescence.

The potential of p53 as a druggable target to induce cellular senescence and suppression of fibrosis is further supported by the observed antifibrotic activity of the drug CX-5461, a novel selective RNA polymerase I inhibitor. Notably, CX-5461 (1 μM) exerts its antifibrotic activity through induction of a DNA damage response, that triggers the activation of the p53 pathway and cellular growth arrest. Importantly, inhibiting p53 with PFT-α (10 μM) or depleting p53 with shRNA blocks these antifibrotic effects of CX-5461[83]. Notably, p53 directly suppresses RNA polymerase I-mediated ribosomal RNA

(rRNA) gene transcription that causes cellular growth arrest [84]. Similarly, Rhein (35 μM), a lipophilic anthraquinone compound, inhibits cellular growth and alleviates fibrogenic gene expression in hypoxia-induced human cardiac fibroblasts, an *in vitro* model of cardiac fibrogenic milieu. Rhein appears to exert its anti-proliferative and anti-fibrotic effects through induction of p53 and its downstream target p21 (Table 1). Mechanistically, Rhein stabilizes p53 by interacting with HDAC3/HDAC5, positioning Rhein as a promising anti-fibrotic candidate acting through the p53 signaling pathway [85]. However, long-term rigorous preclinical studies are essential to evaluate the efficacy and safety of these anti-fibrotic, pro-senescence agents. Collectively, it is reasonable to conclude that pharmacological activation of p53 represents a viable strategy to repress the initiation and progression of fibrogenic events by suppressing collagen gene transcription, activating cell cycle arrest and ultimately promoting cellular senescence.

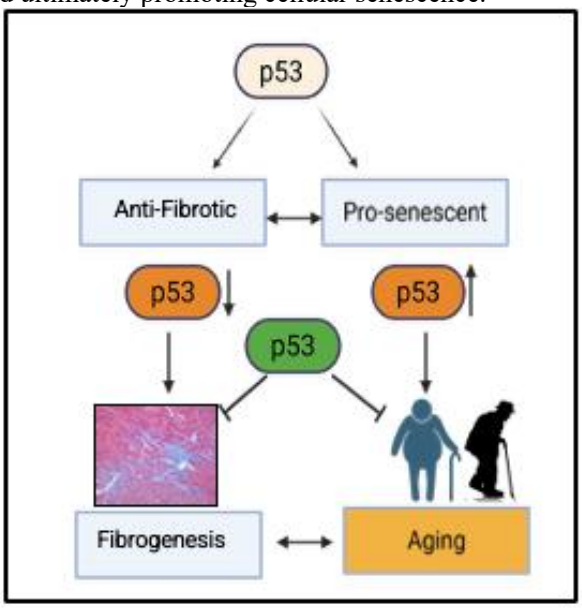

Figure 3. Dual Role of p53 as a Pro-Aging and Anti-Fibrotic Transcription Factor. Control of aging and fibrosis by different levels of p53: Deficiency of p53 is generally associated with worse fibrogenesis due to increased collagen gene transcription and lack of senescence in collagen producing cells. While sustained stress-induced elevated p53 contributes to aging, shuttle activation of p53 [green] acts as anti-fibrotic and anti-aging transcription factor.

5. Concluding Remarks and Future Directions:

The data from cellular and preclinical studies explicitly prove that p53 is a key regulator in controlling stressor-induced cellular senescence and aging on one hand and limiting the extent of fibrogenesis on the other hand [Fig. 3]. Pharmacological or genetic modulation of p53 activity is a viable approach to control the extent of fibrogenesis. This is achieved through direct inhibition of collagen gene transcription and through induction of senescence of matrix protein producing cells by activating p53. Finally, this improves cellular transcriptomic, proteomic and metabolomic profiles suitable for tissue homeostasis. Therefore, p53 activation is beneficial. Because the antifibrotic effects of p53 rely on the magnitude and timing of its activation, a critical question arises: what constitutes the optimal therapeutic strategy? In the setting of stress-induced senescence or aging, the therapeutic goal would ideally be restoration of physiological p53 activity. In contrast, under a fibrogenic milieu, time-dependent suboptimal activation of p53 may limit fibrosis progression without triggering excessive or maladaptive senescence or even apoptosis. Given that p53 is deregulated in a wide variety of cancers, multiple therapeutic approaches have been developed to activate wildtype p53 or reactivate mutant p53. These include MDM2 inhibitors, such as Nutlins, which disrupt the p53–MDM2 interaction, prevent p53 proteasomal degradation, and increase p53 stability, thereby promoting cancer cell growth arrest [22]. Although numerous inhibitors targeting p53–MDM2 interactions have entered clinical trials [21,86], none have gained regulatory approval, primarily due to toxicity related adverse side effects [summarized in 86].

The key unanswered questions for shaping the future of p53 research include: What is the optimal therapeutic window to activate p53 and induce myofibroblast senescence following pro-fibrogenic stress? Current evidence indicates that the early stage of fibrogenesis is highly manageable or even reversible. Therefore, short-term activation of SASP signaling at this stage may be an effective therapeutic window to halt the progression of fibrogenesis. The next question is: How can p53-induced senescent cells be selectively cleared before they propagate senescence to neighboring healthy cells via SASP-mediated paracrine signaling? Although senolytic agents effectively clear most of the senescent cells, they are not suitable for terminally differentiated cardiomyocytes. The lysis and removal of these non-dividing cells would be detrimental to tissue and organ function. Adult cardiomyocytes are non-dividing terminally differentiated, yet they are not exempt from cellular senescence. In response to stressors, cardiomyocytes can activate p53 signaling and acquire senescence-associated phenotypes including expression of senescence regulators and SASP factors. Ultimately, these changes are linked to cardiometabolic disease [87,88]. Protecting them from entering the senescence cascade therefore remains an important unresolved question. Moreover, chronic p53 activation can be harmful. For instance, the pharmacological or genetic overactivation of p53 may trigger premature, irreversible

cellular growth or senescence in the surrounding microenvironment, ultimately accelerating aging in healthy tissues. Both complete loss and excessive activity of p53 are detrimental. Therefore, genetic, or pharmacological, or immunological strategies should be developed to maintain p53 within its physiological range, sufficient to restrain fibrosis and decelerate aging without causing off-target damage. While lower p53 is beneficial for matrix protein collagen synthesis and prevention of senescence during wound healing or reparative fibrosis after myocardial infarction, p53 activation is required to reduce collagen synthesis and reactive fibrogenesis in response to stressors like hypertension.

Because p53 activity declines [23,24] and fibrosis accumulates with age, temporally suboptimal p53 activation using pharmacological or genetic tools may offer a realistic therapeutic avenue to reduce or reverse aging-associated fibrosis. To slow organ aging driven by cellular senescence, senomorphic agents represent a highly attractive therapeutic approach. By suppressing SASP and modulating p53 network activity without inducing cell death or promoting paracrine senescence, these compounds offer a promising strategy to extend healthspan. In contrast, for the amelioration or reversal of advanced fibrosis, the short-term activation of p53 and senescence networks in collagen-producing cells, followed by senomorphic drug therapy will serve as a viable approach. However, a central challenge is the timely suppression of SASP production in p53-induced senescent cells using senomorphic agents, thereby preventing the accumulation of these factors from accelerating inflammation, tissue dysfunction, and organ aging. To develop safe, p53-targeted anti-fibrotic therapies, we must determine target-cell specificity, optimal delivery methods, dosing windows, disease stages, safety markers, and the ultimate fate of senescent-cells. We hope this viewpoint on the interesting dual trajectory of p53 as a pro-senescent and an anti-fibrotic factor opens new avenues for developing age-associated fibrosis therapies to extend healthspan.

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Conflict of Interest

The authors have no conflict of interest to disclose for the content of this
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