Published in final edited form as:
Biogerontology. 2013 December ; 14(6): . doi:10.1007/s10522-013-9451-6.

Mechanistic Links between Aging and Lung Fibrosis

Victor J. Thannickal
Division of Pulmonary, Allergy and Critical Care Medicine, Department of Medicine, University of Alabama at Birmingham

Abstract

Our understanding of the biology of aging has advanced significantly in recent years. This has resulted in the recent formulation of the "hallmarks of aging" that include genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication. Idiopathic pulmonary fibrosis (IPF) is a progressive and fatal lung disease that results from the accumulation of scar tissue in the lungs of affected individuals. IPF is a disease of aging that most commonly affects human subjects older than sixty years of age. While progress has been made in elucidating key pathological processes in IPF, the relationship of these processes to those that occur during aging are not well defined. In this review, we explore existing and emerging paradigms in the pathogenesis of IPF in light of the recently defined hallmarks of aging.

Introduction: Idiopathic Pulmonary Fibrosis is a Disease of Aging

There is uncertainly and debate regarding theories of aging (i.e., why it occurs), its mechanisms (i.e., how it occurs) and whether the process can be influenced to extend lifespan, particularly in humans. Significant progress has been made over the past three decades in our understanding of the biology of aging, recently summarized in a review entitled, the "hallmarks of aging" (Lopez-Otin et al. 2013). While the question of whether lifespan of humans can be extended by pharmacologic interventions or regenerative therapies remains controversial (Warner et al. 2005; de Grey 2005), perhaps less controversial is the proposition that the emerging knowledge of the biology of aging will inform novel therapeutics and interventions for age-related diseases. In this short review, we provide evidence for idiopathic pulmonary fibrosis (IPF) as an age-related disease and explore mechanisms for its pathobiology in light of the recently proposed hallmarks of aging (Lopez-Otin et al. 2013).

IPF is a disease of aging (Raghu et al. 2006; Fell et al. 2010; Collard 2010). The incidence and prevalence of IPF increase almost exponentially with each decade of life; two-thirds of IPF patients are older than 60 years at the time of presentation with a mean age of 66 years at the time of diagnosis (Raghu et al. 2006). Thus, similar to other more common age-related diseases such as cardiovascular disease, neurodegenerative diseases, cancer, osteoporosis, and diabetes, IPF is likely to share common pathophysiologic mechanisms with the aging process, itself (Thannickal and Loyd 2008). The hallmarks of aging include genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication (Lopez-Otin et al. 2013). What is the current evidence that these, often overlapping, processes contribute to the pathobiology of IPF?

Address correspondence to: Victor J. Thannickal, M.D., Division of Pulmonary, Allergy and Critical Care Medicine, University of Alabama at Birmingham, 429 THT, 1900 University Blvd., Birmingham, AL 35294-0006, Phone: 205-975-6376, Fax: 205-934-1721, vjthan@uab.edu.

Genomic Instability

The accumulation of nuclear and mitochondrial DNA damage commonly accompanies the aging process (Moskalev et al. 2013; Park and Larsson 2011). Increased DNA damage has been linked to accelerated aging in a number of progeroid syndromes (Burtner and Kennedy 2010). There is emerging evidence that augmentation of DNA repair mechanisms may prolong lifespan and protect against aging-related disease (Baker et al. 2013). Microsatellite instability and loss of heterozygosity (LOH) are more frequent in IPF (Vassilakis et al. 2000; Ricci et al. 2013). LOH at the homeodomain-interacting protein kinase 2 (HIPK2) gene, which is typically activated by genotoxic stimuli, was reported to underlie apoptosis resistance, specifically of IPF fibroblasts (Ricci et al. 2013).

Proteomic analyses of IPF lung tissue support the activation of a DNA damage response (Korfei et al. 2011). The expression of p53 and p21 are upregulated in association with chronic DNA damage of IPF lung epithelial cells, mediating either G1 arrest or apoptosis (Kuwano et al. 1996). IPF lung epithelial cells also express deltaN-p63 at sites of abnormal proliferation at bronchiolo-alveolar junctions, characterized by epithelial hyperplasia, squamous metaplasia, bronchiolization, and abnormal p53 nuclear accumulation (Chilosi et al. 2002; Chilosi et al. 2003). Mitochondrial DNA repair enzymes such as 8-oxoguanine DNA glycosylase (Ogg1) appear to be activated in asbestos-induced lung fibrosis, presumably in an attempt to counteract oxidative stress and apoptosis of lung epithelial cells (Liu et al. 2010a). Together, these studies indicate that different cell types of the lung show evidence of chronic DNA damage response. Moreover, the observation that lung fibrosis can develop in pediatric patients harboring deficiencies in DNA-repair pathways (Schroeder et al. 2005; Vece et al. 2012; Kropski et al. 2013), further supports the concept of deficiencies in DNA repair pathways contributing to the pathogenesis of IPF.

Telomere Attrition

IPF is now recognized as the most common manifestation of telomere-mediated disorders (Alder et al. 2008; Armanios 2012). Telomerase mutations also are the most frequent cause of familial IPF (Armanios et al. 2007; Armanios 2012, 2013). Shortening of telomeres, in the absence of telomerase mutations, is observed in sporadic cases (Alder et al. 2008; Cronkhite et al. 2008), suggesting that this may be common pathophysiological mechanism resulting from a combination of genetic, environmental, and age-related causes (Thannickal and Loyd 2008).

Pathophysiological mechanisms relating short telomeres to specific cellular phenotypes and fibrogenesis remain to be elucidated. Animal models of injury and fibrosis in mice with telomerase deficiency reveal contradictory findings (Liu et al. 2007; Degryse et al. 2012). Further studies of the role of telomerases and telomere length and their role in specific cell types that participate in lung fibrosis are warranted.

Epigenetic Alterations

A number of epigenetic mechanisms involving histone modifications, DNA methylation, and microRNAs (miRNAs) have been implicated in aging (Rando and Chang 2012). Studies that link epigenetic silencing of anti-fibrotic genes and activation of pro-fibrotic genes have begun to emerge. Epigenetic silencing of the putative “fibrosis suppressor” protein, Thy-1, involves both promoter hypermethylation (Sanders et al. 2008; Robinson et al. 2012) and histone modifications (Sanders et al. 2011). The cyclooxygenase-2 (COX-2) gene that is responsible for production of the anti-fibrotic mediator, prostaglandin E_2 (PGE_2), has been linked to reduced histone H3 and H4 acetylation due to decreased recruitment of histone acetyltransferases (HATs) and increased recruitment of transcriptional corepressor

complexes to the COX-2 promoter (Robinson et al. 2012). The same group subsequently demonstrated that repression of another anti-fibrotic chemokine, interferon-inducible protein of 10 kDa (IP-10), is mediated by histone deacetylation and hypermethylation (Coward et al. 2010). The tumor suppressor gene, $p14^{ARF}$, which mediates anti-apoptotic effects of IPF lung fibroblasts, is silenced by promoter hypermethylation (Cisneros et al. 2012). Since p14ARF induction, as opposed to silencing, is implicated in cellular senescence and aging, the potential cell-specific effects of such epigenetic alterations need to be uncovered. Our group has recently demonstrated that senescent fibroblasts which acquire an apoptosis-resistant phenotype express constitutively high levels of the anti-apoptotic gene, Bcl2, and reduced levels of the anti-apoptotic Bax gene; this altered Bcl-2:Bax ratio is mediated by global and locus-specific histone modifications in senescent fibroblasts (Sanders et al. 2012b). Histone modifications also appear to account for the decreases in Fas expression that confers apoptosis resistance to fibrotic lung fibroblasts (Huang et al. 2013).

DNA methylation patterns are altered in IPF (Sanders et al. 2012a; Rabinovich et al. 2012); however, how these changes relate to the process of aging *per se* is unclear. Similarly, recent studies implicate alterations in the regulation of miRNAs in fibrogenic processes and IPF (Liu et al. 2010b; Cushing et al. 2010; Yang et al. 2012; Dakhlallah et al. 2013). Although miRNAs are increasingly being implicated in age-related diseases (Dimmeler and Nicotera 2013), the interactions between miRNAs and other epigenetic mechanisms that occur in “normal” aging and in specific diseases associated with aging need to be elucidated.

Loss of Proteostasis

The accumulation of unfolded, misfolded or aggregated proteins is a hallmark of many age-related diseases (Powers et al. 2009). Protein quality control is maintained by two major proteolytic systems, the autophagy-lysosomal system and the ubiquitin-proteosomal system, both of which decline with age (Rubinsztein et al. 2011; Koga et al. 2011). There is evidence for unfolded protein response (UPR) and endoplasmic reticulum (ER) stress in alveolar epithelial cells in lungs of patients with familial IPF (Thomas et al. 2002) and sporadic cases (Korfei et al. 2008; Lawson et al. 2008; Korfei et al. 2011). Activation of ER stress in epithelial cells may be mediated by intrinsic abnormalities in protein folding or by extrinsic stress such as viral infections; subsequent apoptosis of epithelial cells may be sufficient to initiate fibrotic remodeling (Sisson et al. 2010). Alternatively, activation of the UPR may induce secretion of the potent pro-fibrotic mediator, transforming growth factor-β1 (TGF-β1) (Maitra et al. 2012).

Recent studies indicate that autophagy is diminished in IPF (Patel et al. 2012; Araya et al. 2013). The mechanisms that lead to deficient autophagy are not well understood, as well as how this leads to the aberrant remodeling response in IPF. Interestingly, while many of the “upstream” reparative pathways, including cellular senescence, are activated in another age-related lung disease, chronic obstructive pulmonary disease (COPD), autophagy is reported to be enhanced in COPD (Chen et al. 2008; Hwang et al. 2010). This suggests that autophagy may function as a critical “switch” in the different tissue remodeling responses to lung injury. One suggested mechanism for decreased autophagy is reduced beclin-1, which is combination with reduced expression of the anti-apoptotic Bcl-2 gene, promotes apoptosis-resistance of fibroblasts (Ricci et al. 2012), implicated in the persistence and progression of IPF (Thannickal and Horowitz 2006). In contrast to the notion that it may be protective in IPF, autophagy has also been suggested as a core pathway driving fibrogenesis (Hernandez-Gea and Friedman 2012). It remains to be determined whether such differences relate to the model system utilized or inter-organ differences.

Deregulated Nutrient Sensing

There is now strong evidence that decreased nutrient signaling extends lifespan in multiple species (reviewed in Fontana et al. 2010). There is proof-of-concept that mimicking a state of nutrient deficiency with the pharmacological inhibitor, rapamycin, is effective in a TGF-α-induced model of lung fibrosis in mice (Korfhagen et al. 2009), although this was not observed in the murine bleomycin model (Madala et al. 2011). Similarly, activating AMP-activated protein kinase (AMPK) with 5-aminoimidazole-4-carboxamide-1-β-4-ribofuranoside (AICAR) or metformin mediates protection from airway inflammation and remodeling (Park et al. 2012). In this study, the expression of fibronectin and collagen was diminished by metformin through AMPK-α1 activation in cultured fibroblasts. Further studies are required to determine precise mechanisms of fibrogenesis by anabolic signaling and potential amelioration of fibrosis by pharmacologic “mimics” of nutrient deficiency.

Mitochondrial dysfunction

The free radical theory of aging is being refined as we gain better understanding of the contextual roles of reactive oxygen species (ROS) in adaptive and maladaptive responses in various tissues (Kirkwood and Kowald 2012). There is evidence for mitochondrial dysfunction in asbestos-related lung fibrosis (Liu et al. 2010a), although less known about the role of mitochondrial function and mitochondria-generated ROS (mtROS) in IPF. However, there is emerging implication of mtROS in TGF-β signaling and expression of pro-fibrotic genes (Jain et al. 2013). Interestingly another ROS-generating enzyme, NADPH oxidase-4 (Nox4) that mediates lung fibrosis (Hecker et al. 2009), has been reported to localize to mitochondria (Block et al. 2009; Crespo et al. 2010). Elucidating the interactions between Nox4 and mitochondrial (dys)function (Koziel et al. 2013; Wolin 2013) in both physiological and pathological states will shed light on their respective (and potentially combined) roles in regulating mitochondrial dynamics, cellular senescence, and fibrosis.

Cellular Senescence

While there is strong evidence that senescent cells accumulate in tissues with aging (Krishnamurthy et al. 2004), the mechanisms by which they contribute to aging and age-related diseases deserves further study. Fibrosis is generally considered as a fibro-“proliferative”, but benign (non-cancerous) disease process. Consistent with this concept, the emergence of senescent fibrogenic cells in the context of wound healing has been proposed to mediate anti-fibrotic effects (Krizhanovsky et al. 2008; Jun and Lau 2010). Thus, similar to its role in tumor-suppression, cellular senescence may function as a mechanism for fibrosis-suppression (Rodier and Campisi 2011). Such “antagonistically pleiotropic” roles of senescence must be reconciled in specific age-related diseases, including IPF, before effective therapeutics targeting senescence pathways can be designed.

Stem Cell Exhaustion

Stem cell exhaustion has been implicated in a number of age-related diseases, including IPF (Chilosi et al. 2010; Chilosi et al. 2013). The principal cells implicated in “stem cell exhaustion” associated with IPF are alveolar type II epithelial cells (Chilosi et al. 2013); however, a hyperplastic response around fibroblastic foci with abnormal bronchiolarization is often seen, an observation that has not been adequately explained. Whether this hyper-proliferative response reflects differences in the susceptibility of distinct groups of airway epithelial stem cells is currently not known. Additionally, a better understanding of stem cell niches that also under aging is required before the potential beneficial effects of stem cell-based therapies for chronic lung diseases can be realized (Mora and Rojas 2013).

Altered Intercellular Communication

There is general consensus among most investigators that fibrosis results from aberrant epithelial-mesenchymal interactions (Thannickal et al. 2004; Chapman 2011). Alterations in and between resident structural cells, immune cells and microbial pathogens (microbiome) occurs during aging (Lopez-Otin et al. 2013), yet how these changes influence the phenotypic expression of fibrosis involving specific organ systems is not understood. Studies on the secretome of (senescent) cells, phenotypic plasticity (or loss thereof), and "inflammaging" (Franceschi et al. 2000) in IPF will illuminate the potential for therapeutic opportunities for this recalcitrant disease process.

Conclusion

IPF is a disease of aging with a progressive and fatal course, and without effective therapies. An understanding of the biology of aging will provide improved understanding of fibrogenesis and its progression; as well inform the design, discovery and development of more effective therapies for this dreadful disease.

Acknowledgments

This work was funded by National Institutes of Health grants, R01 HL067967, R01 HL094230 and P50 HL107181.

References

Alder JK, Chen JJ, Lancaster L, Danoff S, Su SC, Cogan JD, Vulto I, Xie M, Qi X, Tuder RM, Phillips JA 3rd, Lansdorp PM, Loyd JE, Armanios MY. Short telomeres are a risk factor for idiopathic pulmonary fibrosis. Proc Natl Acad Sci U S A. 2008; 105 (35):13051–13056. 0804280105 [pii]. 10.1073/pnas.0804280105 [PubMed: 18753630]

Araya J, Kojima J, Takasaka N, Ito S, Fujii S, Hara H, Yanagisawa H, Kobayashi K, Tsurushige C, Kawaishi M, Kamiya N, Hirano J, Odaka M, Morikawa T, Nishimura SL, Kawabata Y, Hano H, Nakayama K, Kuwano K. Insufficient autophagy in idiopathic pulmonary fibrosis. Am J Physiol Lung Cell Mol Physiol. 2013; 304 (1):L56–69.10.1152/ajplung.00213.2012 [PubMed: 23087019]

Armanios M. Telomerase and idiopathic pulmonary fibrosis. Mutat Res. 2012; 730 (1–2):52–58.10.1016/j.mrfmmm.2011.10.013 [PubMed: 22079513]

Armanios M. Telomeres and age-related disease: how telomere biology informs clinical paradigms. J Clin Invest. 2013; 123 (3):996–1002.10.1172/JCI66370 [PubMed: 23454763]

Armanios MY, Chen JJ, Cogan JD, Alder JK, Ingersoll RG, Markin C, Lawson WE, Xie M, Vulto I, Phillips JA 3rd, Lansdorp PM, Greider CW, Loyd JE. Telomerase mutations in families with idiopathic pulmonary fibrosis. N Engl J Med. 2007; 356 (13):1317–1326. 356/13/1317 [pii]. 10.1056/NEJMoa066157 [PubMed: 17392301]

Baker DJ, Dawlaty MM, Wijshake T, Jeganathan KB, Malureanu L, van Ree JH, Crespo-Diaz R, Reyes S, Seaburg L, Shapiro V, Behfar A, Terzic A, van de Sluis B, van Deursen JM. Increased expression of BubR1 protects against aneuploidy and cancer and extends healthy lifespan. Nat Cell Biol. 2013; 15 (1):96–102.10.1038/ncb2643 [PubMed: 23242215]

Block K, Gorin Y, Abboud HE. Subcellular localization of Nox4 and regulation in diabetes. Proc Natl Acad Sci U S A. 2009; 106 (34):14385–14390.10.1073/pnas.0906805106 [PubMed: 19706525]

Burtner CR, Kennedy BK. Progeria syndromes and ageing: what is the connection? Nat Rev Mol Cell Biol. 2010; 11 (8):567–578.10.1038/nrm2944 [PubMed: 20651707]

Chapman HA. Epithelial-mesenchymal interactions in pulmonary fibrosis. Annu Rev Physiol. 2011; 73:413–435.10.1146/annurev-physiol-012110-142225 [PubMed: 21054168]

Chen ZH, Kim HP, Sciurba FC, Lee SJ, Feghali-Bostwick C, Stolz DB, Dhir R, Landreneau RJ, Schuchert MJ, Yousem SA, Nakahira K, Pilewski JM, Lee JS, Zhang Y, Ryter SW, Choi AM. Egr-1 regulates autophagy in cigarette smoke-induced chronic obstructive pulmonary disease. PLoS One. 2008; 3 (10):e3316.10.1371/journal.pone.0003316 [PubMed: 18830406]

Chilosi M, Carloni A, Rossi A, Poletti V. Premature lung aging and cellular senescence in the pathogenesis of idiopathic pulmonary fibrosis and COPD/emphysema. Translational research : the journal of laboratory and clinical medicine. 201310.1016/j.trsl.2013.06.004

Chilosi M, Doglioni C, Murer B, Poletti V. Epithelial stem cell exhaustion in the pathogenesis of idiopathic pulmonary fibrosis. Sarcoidosis Vasc Diffuse Lung Dis. 2010; 27 (1):7–18. [PubMed: 21086900]

Chilosi M, Poletti V, Murer B, Lestani M, Cancellieri A, Montagna L, Piccoli P, Cangi G, Semenzato G, Doglioni C. Abnormal re-epithelialization and lung remodeling in idiopathic pulmonary fibrosis: the role of deltaN-p63. Lab Invest. 2002; 82 (10):1335–1345. [PubMed: 12379768]

Chilosi M, Poletti V, Zamo A, Lestani M, Montagna L, Piccoli P, Pedron S, Bertaso M, Scarpa A, Murer B, Cancellieri A, Maestro R, Semenzato G, Doglioni C. Aberrant Wnt/beta-catenin pathway activation in idiopathic pulmonary fibrosis. Am J Pathol. 2003; 162 (5):1495–1502. [PubMed: 12707032]

Cisneros J, Hagood J, Checa M, Ortiz-Quintero B, Negreros M, Herrera I, Ramos C, Pardo A, Selman M. Hypermethylation-mediated silencing of p14(ARF) in fibroblasts from idiopathic pulmonary fibrosis. Am J Physiol Lung Cell Mol Physiol. 2012; 303 (4):L295–303.10.1152/ajplung.00332.2011 [PubMed: 22707614]

Collard HR. The age of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2010; 181 (8):771–772.10.1164/rccm.201001-0049ED [PubMed: 20382799]

Coward WR, Watts K, Feghali-Bostwick CA, Jenkins G, Pang L. Repression of IP-10 by interactions between histone deacetylation and hypermethylation in idiopathic pulmonary fibrosis. Mol Cell Biol. 2010; 30 (12):2874–2886.10.1128/MCB.01527-09 [PubMed: 20404089]

Crespo FL, Sobrado VR, Gomez L, Cervera AM, McCreath KJ. Mitochondrial reactive oxygen species mediate cardiomyocyte formation from embryonic stem cells in high glucose. Stem Cells. 2010; 28 (7):1132–1142.10.1002/stem.441 [PubMed: 20506541]

Cronkhite JT, Xing C, Raghu G, Chin KM, Torres F, Rosenblatt RL, Garcia CK. Telomere shortening in familial and sporadic pulmonary fibrosis. Am J Respir Crit Care Med. 2008; 178 (7):729–737. 200804-550OC [pii]. 10.1164/rccm.200804-550OC [PubMed: 18635888]

Cushing L, Kuang PP, Qian J, Shao F, Wu J, Little F, Thannickal VJ, Cardoso WV, Lu J. MIR-29 is a Major Regulator of Genes Associated with Pulmonary Fibrosis. Am J Respir Cell Mol Biol. 2010 2010–0323OC [pii]. 10.1165/rcmb.2010-0323OC

Dakhlallah D, Batte K, Wang Y, Cantemir-Stone CZ, Yan P, Nuovo G, Mikhail A, Hitchcock CL, Wright VP, Nana-Sinkam SP, Piper MG, Marsh CB. Epigenetic regulation of miR-17~92 contributes to the pathogenesis of pulmonary fibrosis. Am J Respir Crit Care Med. 2013; 187 (4): 397–405.10.1164/rccm.201205-0888OC [PubMed: 23306545]

de Grey AD. Resistance to debate on how to postpone ageing is delaying progress and costing lives. Open discussions in the biogerontology community would attract public interest and influence funding policy. EMBO reports. 2005; 6(Spec No):S49–53.10.1038/sj.embor.7400399 [PubMed: 15995663]

Degryse AL, Xu XC, Newman JL, Mitchell DB, Tanjore H, Polosukhin VV, Jones BR, McMahon FB, Gleaves LA, Phillips JA 3rd, Cogan JD, Blackwell TS, Lawson WE. Telomerase deficiency does not alter bleomycin-induced fibrosis in mice. Exp Lung Res. 2012; 38 (3):124–134.10.3109/01902148.2012.658148 [PubMed: 22394286]

Dimmeler S, Nicotera P. MicroRNAs in age-related diseases. EMBO molecular medicine. 2013; 5 (2): 180–190.10.1002/emmm.201201986 [PubMed: 23339066]

Fell CD, Martinez FJ, Liu LX, Murray S, Han MK, Kazerooni EA, Gross BH, Myers J, Travis WD, Colby TV, Toews GB, Flaherty KR. Clinical predictors of a diagnosis of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2010; 181 (8):832–837.10.1164/rccm.200906-0959OC [PubMed: 20056903]

Fontana L, Partridge L, Longo VD. Extending healthy life span--from yeast to humans. Science. 2010; 328 (5976):321–326.10.1126/science.1172539 [PubMed: 20395504]

Franceschi C, Bonafe M, Valensin S, Olivieri F, De Luca M, Ottaviani E, De Benedictis G. Inflamm-aging. An evolutionary perspective on immunosenescence. Ann N Y Acad Sci. 2000; 908:244–254. [PubMed: 10911963]

Hecker L, Vittal R, Jones T, Jagirdar R, Luckhardt TR, Horowitz JC, Pennathur S, Martinez FJ, Thannickal VJ. NADPH oxidase-4 mediates myofibroblast activation and fibrogenic responses to lung injury. Nat Med. 2009; 15 (9):1077–1081. nm.2005 [pii]. 10.1038/nm.2005 [PubMed: 19701206]

Hernandez-Gea V, Friedman SL. Autophagy fuels tissue fibrogenesis. Autophagy. 2012; 8 (5):849–850.10.4161/auto.19947 [PubMed: 22617442]

Huang SK, Scruggs AM, Donaghy J, Horowitz JC, Zaslona Z, Przybranowski S, White ES, Peters-Golden M. Histone modifications are responsible for decreased Fas expression and apoptosis resistance in fibrotic lung fibroblasts. Cell death & disease. 2013; 4:e621.10.1038/cddis.2013.146 [PubMed: 23640463]

Hwang JW, Chung S, Sundar IK, Yao H, Arunachalam G, McBurney MW, Rahman I. Cigarette smoke-induced autophagy is regulated by SIRT1-PARP-1-dependent mechanism: implication in pathogenesis of COPD. Arch Biochem Biophys. 2010; 500 (2):203–209.10.1016/j.abb.2010.05.013 [PubMed: 20493163]

Jain M, Rivera S, Monclus EA, Synenki L, Zirk A, Eisenbart J, Feghali-Bostwick C, Mutlu GM, Budinger GR, Chandel NS. Mitochondrial reactive oxygen species regulate transforming growth factor-beta signaling. J Biol Chem. 2013; 288 (2):770–777.10.1074/jbc.M112.431973 [PubMed: 23204521]

Jun JI, Lau LF. The matricellular protein CCN1 induces fibroblast senescence and restricts fibrosis in cutaneous wound healing. Nat Cell Biol. 2010; 12 (7):676–685.10.1038/ncb2070 [PubMed: 20526329]

Kirkwood TB, Kowald A. The free-radical theory of ageing--older, wiser and still alive: modelling positional effects of the primary targets of ROS reveals new support. Bioessays. 2012; 34 (8):692–700.10.1002/bies.201200014 [PubMed: 22641614]

Koga H, Kaushik S, Cuervo AM. Protein homeostasis and aging: The importance of exquisite quality control. Ageing research reviews. 2011; 10 (2):205–215.10.1016/j.arr.2010.02.001 [PubMed: 20152936]

Korfei M, Ruppert C, Mahavadi P, Henneke I, Markart P, Koch M, Lang G, Fink L, Bohle RM, Seeger W, Weaver TE, Guenther A. Epithelial endoplasmic reticulum stress and apoptosis in sporadic idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2008; 178 (8):838–846. 200802-313OC [pii]. 10.1164/rccm.200802-313OC [PubMed: 18635891]

Korfei M, Schmitt S, Ruppert C, Henneke I, Markart P, Loeh B, Mahavadi P, Wygrecka M, Klepetko W, Fink L, Bonniaud P, Preissner KT, Lochnit G, Schaefer L, Seeger W, Guenther A. Comparative proteomic analysis of lung tissue from patients with idiopathic pulmonary fibrosis (IPF) and lung transplant donor lungs. J Proteome Res. 2011; 10 (5):2185–2205.10.1021/pr1009355 [PubMed: 21319792]

Korfhagen TR, Le Cras TD, Davidson CR, Schmidt SM, Ikegami M, Whitsett JA, Hardie WD. Rapamycin prevents transforming growth factor-alpha-induced pulmonary fibrosis. Am J Respir Cell Mol Biol. 2009; 41 (5):562–572.10.1165/rcmb.2008-0377OC [PubMed: 19244201]

Koziel R, Pircher H, Kratochwil M, Lener B, Hermann M, Dencher NA, Jansen-Durr P. Mitochondrial respiratory chain complex I is inactivated by NADPH oxidase Nox4. Biochem J. 2013; 452 (2):231–239.10.1042/BJ20121778 [PubMed: 23514110]

Krishnamurthy J, Torrice C, Ramsey MR, Kovalev GI, Al-Regaiey K, Su L, Sharpless NE. Ink4a/Arf expression is a biomarker of aging. J Clin Invest. 2004; 114 (9):1299–1307.10.1172/JCI22475 [PubMed: 15520862]

Krizhanovsky V, Yon M, Dickins RA, Hearn S, Simon J, Miething C, Yee H, Zender L, Lowe SW. Senescence of activated stellate cells limits liver fibrosis. Cell. 2008; 134 (4):657–667. S0092-8674(08)00836-2 [pii]. 10.1016/j.cell.2008.06.049 [PubMed: 18724938]

Kropski JA, Lawson WE, Young LR, Blackwell TS. Genetic studies provide clues on the pathogenesis of idiopathic pulmonary fibrosis. Disease models & mechanisms. 2013; 6 (1):9–17.10.1242/dmm.010736 [PubMed: 23268535]

Kuwano K, Kunitake R, Kawasaki M, Nomoto Y, Hagimoto N, Nakanishi Y, Hara N. P21Waf1/Cip1/Sdi1 and p53 expression in association with DNA strand breaks in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 1996; 154 (2 Pt 1):477–483.10.1164/ajrccm.154.2.8756825 [PubMed: 8756825]

Lawson WE, Crossno PF, Polosukhin VV, Roldan J, Cheng DS, Lane KB, Blackwell TR, Xu C, Markin C, Ware LB, Miller GG, Loyd JE, Blackwell TS. Endoplasmic reticulum stress in alveolar epithelial cells is prominent in IPF: association with altered surfactant protein processing and herpesvirus infection. Am J Physiol Lung Cell Mol Physiol. 2008; 294 (6):L1119–1126. 00382.2007 [pii]. 10.1152/ajplung.00382.2007 [PubMed: 18390830]

Liu G, Beri R, Mueller A, Kamp DW. Molecular mechanisms of asbestos-induced lung epithelial cell apoptosis. Chemico-biological interactions. 2010a; 188 (2):309–318.10.1016/j.cbi.2010.03.047 [PubMed: 20380827]

Liu G, Friggeri A, Yang Y, Milosevic J, Ding Q, Thannickal VJ, Kaminski N, Abraham E. miR-21 mediates fibrogenic activation of pulmonary fibroblasts and lung fibrosis. J Exp Med. 2010b; 207 (8):1589–1597. jem.20100035 [pii]. 10.1084/jem.20100035 [PubMed: 20643828]

Liu T, Chung MJ, Ullenbruch M, Yu H, Jin H, Hu B, Choi YY, Ishikawa F, Phan SH. Telomerase activity is required for bleomycin-induced pulmonary fibrosis in mice. J Clin Invest. 2007; 117 (12):3800–3809.10.1172/JCI32369 [PubMed: 18008008]

Lopez-Otin C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell. 2013; 153 (6):1194–1217.10.1016/j.cell.2013.05.039 [PubMed: 23746838]

Madala SK, Maxfield MD, Davidson CR, Schmidt SM, Garry D, Ikegami M, Hardie WD, Glasser SW. Rapamycin Regulates Bleomycin-Induced Lung Damage in SP-C-Deficient Mice. Pulm Med. 2011; 2011:653524.10.1155/2011/653524 [PubMed: 21660239]

Maitra M, Cano CA, Garcia CK. Mutant surfactant A2 proteins associated with familial pulmonary fibrosis and lung cancer induce TGF-beta1 secretion. Proc Natl Acad Sci U S A. 2012; 109 (51): 21064–21069.10.1073/pnas.1217069110 [PubMed: 23223528]

Mora AL, Rojas M. Adult stem cells for chronic lung diseases. Respirology. 201310.1111/resp.12112

Moskalev AA, Shaposhnikov MV, Plyusnina EN, Zhavoronkov A, Budovsky A, Yanai H, Fraifeld VE. The role of DNA damage and repair in aging through the prism of Koch-like criteria. Ageing research reviews. 2013; 12 (2):661–684.10.1016/j.arr.2012.02.001 [PubMed: 22353384]

Park CB, Larsson NG. Mitochondrial DNA mutations in disease and aging. J Cell Biol. 2011; 193 (5): 809–818.10.1083/jcb.201010024 [PubMed: 21606204]

Park CS, Bang BR, Kwon HS, Moon KA, Kim TB, Lee KY, Moon HB, Cho YS. Metformin reduces airway inflammation and remodeling via activation of AMP-activated protein kinase. Biochemical pharmacology. 2012; 84 (12):1660–1670.10.1016/j.bcp.2012.09.025 [PubMed: 23041647]

Patel AS, Lin L, Geyer A, Haspel JA, An CH, Cao J, Rosas IO, Morse D. Autophagy in idiopathic pulmonary fibrosis. PLoS One. 2012; 7 (7):e41394.10.1371/journal.pone.0041394 [PubMed: 22815997]

Powers ET, Morimoto RI, Dillin A, Kelly JW, Balch WE. Biological and chemical approaches to diseases of proteostasis deficiency. Annual review of biochemistry. 2009; 78:959–991.10.1146/annurev.biochem.052308.114844

Rabinovich EI, Kapetanaki MG, Steinfeld I, Gibson KF, Pandit KV, Yu G, Yakhini Z, Kaminski N. Global methylation patterns in idiopathic pulmonary fibrosis. PLoS One. 2012; 7 (4):e33770.10.1371/journal.pone.0033770 [PubMed: 22506007]

Raghu G, Weycker D, Edelsberg J, Bradford WZ, Oster G. Incidence and prevalence of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2006; 174 (7):810–816. 200602-163OC [pii]. 10.1164/rccm.200602-163OC [PubMed: 16809633]

Rando TA, Chang HY. Aging, rejuvenation, and epigenetic reprogramming: resetting the aging clock. Cell. 2012; 148 (1–2):46–57.10.1016/j.cell.2012.01.003 [PubMed: 22265401]

Ricci A, Cherubini E, Scozzi D, Pietrangeli V, Tabbi L, Raffa S, Leone L, Visco V, Torrisi MR, Bruno P, Mancini R, Ciliberto G, Terzano C, Mariotta S. Decreased expression of autophagic beclin 1 protein in idiopathic pulmonary fibrosis fibroblasts. J Cell Physiol. 201210.1002/jcp.24307

Ricci A, Cherubini E, Ulivieri A, Lavra L, Sciacchitano S, Scozzi D, Mancini R, Ciliberto G, Bartolazzi A, Bruno P, Graziano P, Mariotta S. Homeodomain-interacting protein kinase2 in human idiopathic pulmonary fibrosis. J Cell Physiol. 2013; 228 (1):235–241.10.1002/jcp.24129 [PubMed: 22689412]

Robinson CM, Neary R, Levendale A, Watson CJ, Baugh JA. Hypoxia-induced DNA hypermethylation in human pulmonary fibroblasts is associated with Thy-1 promoter methylation

and the development of a pro-fibrotic phenotype. Respir Res. 2012; 13:74.10.1186/1465-9921-13-74 [PubMed: 22938014]

Rodier F, Campisi J. Four faces of cellular senescence. J Cell Biol. 2011; 192 (4):547–556.10.1083/jcb.201009094 [PubMed: 21321098]

Rubinsztein DC, Marino G, Kroemer G. Autophagy and aging. Cell. 2011; 146 (5):682–695.10.1016/j.cell.2011.07.030 [PubMed: 21884931]

Sanders YY, Ambalavanan N, Halloran B, Zhang X, Liu H, Crossman DK, Bray M, Zhang K, Thannickal VJ, Hagood JS. Altered DNA methylation profile in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2012a; 186 (6):525–535.10.1164/rccm.201201-0077OC [PubMed: 22700861]

Sanders YY, Liu H, Zhang X, Bernard K, Hecker L, Desai L, Liu G, Thannickal VJ. Histone Modifications in Senescence-Associated Resistance to Apoptosis by Oxidative Stress. Redox Biology. 2012b In Press.

Sanders YY, Pardo A, Selman M, Nuovo GJ, Tollefsbol TO, Siegal GP, Hagood JS. Thy-1 promoter hypermethylation: a novel epigenetic pathogenic mechanism in pulmonary fibrosis. Am J Respir Cell Mol Biol. 2008; 39 (5):610–618.10.1165/rcmb.2007-0322OC [PubMed: 18556592]

Sanders YY, Tollefsbol TO, Varisco BM, Hagood JS. Epigenetic regulation of thy-1 by histone deacetylase inhibitor in rat lung fibroblasts. Am J Respir Cell Mol Biol. 2011; 45 (1):16–23.10.1165/rcmb.2010-0154OC [PubMed: 20724553]

Schroeder SA, Swift M, Sandoval C, Langston C. Interstitial lung disease in patients with ataxia-telangiectasia. Pediatr Pulmonol. 2005; 39 (6):537–543.10.1002/ppul.20209 [PubMed: 15789441]

Sisson TH, Mendez M, Choi K, Subbotina N, Courey A, Cunningham A, Dave A, Engelhardt JF, Liu X, White ES, Thannickal VJ, Moore BB, Christensen PJ, Simon RH. Targeted injury of type II alveolar epithelial cells induces pulmonary fibrosis. Am J Respir Crit Care Med. 2010; 181 (3):254–263. 200810-1615OC [pii]. 10.1164/rccm.200810-1615OC [PubMed: 19850947]

Thannickal VJ, Horowitz JC. Evolving concepts of apoptosis in idiopathic pulmonary fibrosis. Proc Am Thorac Soc. 2006; 3 (4):350–356. 3/4/350 [pii]. 10.1513/pats.200601-001TK [PubMed: 16738200]

Thannickal VJ, Loyd JE. Idiopathic pulmonary fibrosis: a disorder of lung regeneration? Am J Respir Crit Care Med. 2008; 178 (7):663–665. 178/7/663 [pii]. 10.1164/rccm.200807-1127ED [PubMed: 18796651]

Thannickal VJ, Toews GB, White ES, Lynch JP 3rd, Martinez FJ. Mechanisms of pulmonary fibrosis. Annu Rev Med. 2004; 55:395–417.10.1146/annurev.med.55.091902.103810 [PubMed: 14746528]

Thomas AQ, Lane K, Phillips J 3rd, Prince M, Markin C, Speer M, Schwartz DA, Gaddipati R, Marney A, Johnson J, Roberts R, Haines J, Stahlman M, Loyd JE. Heterozygosity for a surfactant protein C gene mutation associated with usual interstitial pneumonitis and cellular nonspecific interstitial pneumonitis in one kindred. Am J Respir Crit Care Med. 2002; 165 (9):1322–1328.10.1164/rccm.200112-123OC [PubMed: 11991887]

Vassilakis DA, Sourvinos G, Spandidos DA, Siafakas NM, Bouros D. Frequent genetic alterations at the microsatellite level in cytologic sputum samples of patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2000; 162 (3 Pt 1):1115–1119.10.1164/ajrccm.162.3.9911119 [PubMed: 10988139]

Vece TJ, Schecter MG, Gatti RA, Tunuguntla R, Garcia CK, Langston C, Dishop MK, Moore RH, Fan LL. Rapid and progressive pulmonary fibrosis in 2 families with DNA repair deficiencies of undetermined etiology. The Journal of pediatrics. 2012; 160 (4):700–702. e703.10.1016/j.jpeds.2011.12.001 [PubMed: 22240110]

Warner H, Anderson J, Austad S, Bergamini E, Bredesen D, Butler R, Carnes BA, Clark BF, Cristofalo V, Faulkner J, Guarente L, Harrison DE, Kirkwood T, Lithgow G, Martin G, Masoro E, Melov S, Miller RA, Olshansky SJ, Partridge L, Pereira-Smith O, Perls T, Richardson A, Smith J, von Zglinicki T, Wang E, Wei JY, Williams TF. Science fact and the SENS agenda. What can we reasonably expect from ageing research? EMBO reports. 2005; 6 (11):1006–1008.10.1038/sj.embor.7400555 [PubMed: 16264422]

Wolin MS. Evidence for novel aspects of Nox4 oxidase regulation of mitochondrial function and peroxide generation in an endothelial cell model of senescence. Biochem J. 2013; 452 (2):e1–2.10.1042/BJ20130484 [PubMed: 23662809]

Yang S, Banerjee S, de Freitas A, Sanders YY, Ding Q, Matalon S, Thannickal VJ, Abraham E, Liu G. Participation of miR-200 in pulmonary fibrosis. Am J Pathol. 2012; 180 (2):484–493.10.1016/j.ajpath.2011.10.005 [PubMed: 22189082]