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Systemic Sclerosis-Associated Fibrosis: An Accelerated Aging Phenotype?

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Abstract

Purpose of this review—Systemic sclerosis (SSc) is an autoimmune disease with fibrosis seen in multiple organs. While not traditionally regarded as a disease of aging, SSc-associated fibrosis shares many of the hallmarks of aging seen in other age-related fibrotic disorders. Here, we review current literature of the potential role of aging and age-related cellular processes in the development of SSc and fibrosis.

Recent findings—Accumulating evidence supports a role for immune dysregulation, epigenetic modifications, cellular senescence, mitochondrial dysregulation and impaired autophagy in fibrosis that occurs in aging and SSc.

Summary—Cellular alterations linked to aging may promote the development and/or progression of SSc-associated fibrosis.

Keywords

Systemic Sclerosis; Fibrosis; Aging

Introduction

Systemic sclerosis (SSc) is a systemic autoimmune disease that often leads to fibrosis in multiple organs, including the skin, heart, vasculature and lungs. Progressive organ fibrosis, particularly in the vasculature and lungs, are major contributors to scleroderma mortality (1). There are several mechanisms which contribute to fibrosis in SSc patients including endothelial dysfunction, innate and adaptive immune responses, endoplasmic reticulum (ER) stress and fibroblast activation (2). SSc is not typically considered as a disease of aging, but in a recent large United States cohort, the peak incidence for SSc was between 45 and 64 years of age (3). Older patients with SSc have increased mortality (4, 5), and patients who present at an older age (>65 years) are at increased risk of pulmonary hypertension, muscle weakness, renal impairment, pulmonary disease and cardiac disease (6, 7).

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Conflicts of interest

None

Much of the literature on fibrosis and aging comes from studies examining other fibrotic diseases, specifically idiopathic pulmonary fibrosis (IPF). IPF is a disease which causes progressive lung fibrosis and is seen almost exclusively in the elderly population (8). The patterns of lung disease seen in SSc and IPF are often different. In IPF, the defining histopathologic pattern is usual interstitial pneumonitis (UIP). In SSc patients, a pattern of non-specific interstitial pneumonitis (NSIP) is more common, although UIP is seen in more advanced cases (9). Despite these differences, both SSc and IPF share many pathobiologic features; these include epithelial and endothelial injury, immune dysregulation, and activated fibroblasts with increased deposition of extracellular matrix (10).

Several hallmarks of cellular aging have been proposed including, genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion and altered intercellular communication (11–13). In this manuscript, we explore associations between aging and the pathogenesis of SSc. In particular, we focus on recent studies that highlight the potential role of alterations in immune dysregulation, epigenetic modifications, cellular senescence, mitochondrial dysfunction and impaired autophagy, which are likely to contribute to fibrotic progression in SSc patients.

Immune dysregulation

There is growing evidence of age-related changes in the immune system that lead to immunosenescence (14–16). These changes occur both in the innate and adaptive immune system, and increase susceptibility to infection while decreasing tolerance to self-antigens. Immunosenescence may promote fibrosis in several ways. Immunosenescence can lead to a chronic pro-inflammatory environment (“inflamm-aging”) with increased production of cytokines such as IL-6 and TNF α , and increased levels of neutrophils with enhanced production of reactive oxygen species (ROS). There are also age-related changes in lymphocyte function that might promote a pro-fibrotic environment (16).

There is limited evidence demonstrating a role for immunosenescence in the pathogenesis of SSc. It has been shown that patients with diverse autoimmune disorders, including SSc, are characterized by accelerated aging of the immune system with a decline in T-cell excision circle (TREC) numbers, suggesting increased thymic involution; loss of CD28 expression on both CD4+ and CD8+ T-lymphocytes is a marker of premature aging of lymphocytes in patients with autoimmune disease (17). These CD28^{null} cells are terminally differentiated memory T-cells that are cytotoxic and pro-inflammatory, and are resistant to apoptosis (18, 19). A recent study by Rodriguez-Carrio *et al* has linked a TNF α polymorphism, TNF α rs1800629n (–308 G>A), which is associated with increased production of TNF α and immunosenescence in patients with rheumatoid arthritis. This polymorphism is also associated with increased numbers of CD4+CD28^{null} cells which correlates with worsening clinical outcomes, and it appears that the “immunosenescence phenotype” is reversible with TNF α antagonists ^{**}(18). Interestingly, systemic lupus erythematosus patients have also been shown to exhibit immunosenescence with an imbalance in CD4+ T-lymphocytes, and this correlates with an increase incidence in the metabolic syndrome in these patients ^{*}(20).

While there is evidence of age-related changes in the adaptive immune system in patients with autoimmune disease and pulmonary fibrosis (16–18, 20), the precise mechanisms by which these changes promote fibrosis are unclear. In a recent study by Pinto *et al* (21), age-related changes in the innate immune system that drive fibrosis are beginning to be elucidated. This group of investigators demonstrated that changes in the composition, gene expression and functionality of cardiac tissue macrophages with aging, increases susceptibility in mice to age-related cardiac fibrosis ^{**}(21). This accumulation of macrophages with low CX3CR1 expression in aged mice is associated with an increase in pro-fibrotic gene expression, including MMP9 and CCL24 (21).

Our understanding of immunosenescence and how age-related changes in both the innate and adaptive immune systems promote fibrosis is still evolving. Understanding how aging triggers self-tolerance, impairs resolution of inflammation and the development/progression of fibrosis will be likely be pivotal in developing novel therapeutics that prevent/impede fibrosis.

Epigenetic Modifications

Epigenetic modifications regulate gene expression without changes to the DNA sequence; these include changes in chromatin structure by DNA methylation and histone modifications, as well as changes to coding and non-coding RNAs. There are examples across multiple species that epigenetic modifications influence longevity, aging, age-related diseases (22).

There is increasing evidence for a role of epigenetic modifications in the pathogenesis of SSc. DNA methylation abnormalities have been demonstrated in fibroblasts, endothelial cells and lymphocytes isolated from SSc patients, and histone modifications have been reported in fibroblasts and B-lymphocytes (23). There is also increasing evidence of role of miRNAs in the pathogenesis of SSc (23).

Sirtuin-1 (Sirt1) is a class III histone deacetylase that regulates the transcription of a large number of genes, primarily through transcriptional repression (24, 25). Two recent studies have highlighted the role of Sirt1 in TGF β signaling and the development of SSc-associated fibrosis. Zerr *et al* ^{**}(24) demonstrated that dermal fibroblasts from patients with SSc have decreased levels of Sirt1 when compared to controls, a finding that was replicated in a mouse model of skin fibrosis. In this study, activation of Sirt1 enhanced TGF β signaling and promoted differentiation of fibroblasts into myofibroblasts. Deletion of Sirt1, specifically in fibroblast-like cells, abrogated the effects of TGF β signaling and led to decreased skin fibrosis (24). Similar results were reported by Wei *et al* ^{**}(25) who demonstrated decreased expression of Sirt1 in skin biopsies and dermal fibroblasts from SSc patients, and inhibition of Sirt1 mediated anti-fibrotic effects in a mouse model of skin fibrosis. Together, these studies support an anti-fibrotic role for Sirt1 and suggest that therapeutic approaches inducing/activating Sirt1 may be beneficial in SSc-associated fibrosis.

NADPH oxidase 4 (Nox4) is a member of the NADPH oxidase family of enzymes that generate ROS for cellular signaling; Nox4 has been implicated in oxidative stress responses and fibrosis in multiple models of fibrosis, including SSc (26–30). In recent work examining

epigenetic modification of lung fibroblasts, it was demonstrated that histone modifications involving H4K16Ac mediates age-related increases in Nox4 ^{*}(31); additionally, the histone deacetylase inhibitor, suberoylanilide hydroxamic acid (SAHA) leads to apoptosis of myofibroblasts and decreases lung fibrosis in the murine bleomycin-induced model of lung fibrosis ^{*}(32).

Both canonical and non-canonical Wnt/ β -catenin pathways have been implicated in a variety of fibrotic diseases, including SSc (33). Dees *et al* (34) recently demonstrated that Wnt signaling is increased in leukocytes and fibroblasts of SSc patients by epigenetic down-regulation of the Wnt antagonists, DKK1 and SFRP1; pharmacologic inhibition of methylation-induced silencing of these antagonists led to a decrease in Wnt signaling.

In summary, age-associated epigenetic modifications can lead to activation of SSc fibroblasts to promote fibrosis. Understanding the role of epigenetic modifications in SSc has the potential to lead to novel anti-fibrotic therapies.

Cellular Senescence

Senescence is a complex process that is defined by an acquisition of irreversible growth arrest; importantly, the accumulation of senescent cells in aging and age-related diseases may have profound implications for tissue homeostasis (35). Critical to the pleiotropic actions of senescent cells is the maintenance of high metabolic activity and elaboration of senescence-associated secretory phenotype (SASP). Interestingly, the SASP associated with senescent fibroblasts has been suggested to promote termination of the wound healing response and mediate anti-fibrotic effects in animal models of liver fibrosis ^{**}(36). In contrast, Hecker *et al* ^{*}(30) show that in aged mice with bleomycin-induced lung injury, accumulation of senescent and apoptosis-resistant myofibroblasts is associated with non-resolving fibrosis up to 4 months following injury. In this study, senescence of myofibroblasts was shown to be mediated by an up-regulation of the ROS-generating enzyme, Nox4, and an impaired activation of the Nrf2 antioxidant response pathway; this redox imbalance leads to prolonged senescence and apoptosis resistance leading to persistent fibrosis. Thus, it is important to recognize the differences between acute and chronic senescence in the context of tissue injury-repair (37). Currently, there are limited studies of the role of cellular senescence in the different cell types, including endothelial cells, fibroblasts and immune cells that participate in the pathogenesis of SSc; future studies in this area may provide additional clues to the specific role(s) of senescence in SSc-associated skin and lung fibrosis (38).

Mitochondrial Dysfunction

Decreases in mitochondrial number and mass, changes in mitochondrial DNA and protein levels, and decline in respiratory capacity have all been described in normal aging (39, 40). It is unclear whether this renders cells vulnerable to stress and contributes to disease processes in aging individuals or whether this is a survival mechanism in reparative/regenerative cells (40). There is increasing evidence that mitochondria-generated ROS (mtROS) is important in the pathogenesis of fibrosis (11).

PTEN-induced putative kinase 1 (PINK1) is required for the induction of mitochondrial autophagy (mitophagy) and clearance of damaged/dysfunctional mitochondria. When mitochondria become depolarized, PINK1 accumulates on the surface and begins a signaling cascade that leads to mitophagy (41). PINK1 is also critical for normal mitochondrial function and a deficiency in PINK1 has been linked to dysfunction of the electron transport chain, increased oxidative stress and cellular apoptosis (42). Recent evidence indicates that PINK1 and mitochondrial dysfunction contributes to the pathogenesis of pulmonary fibrosis. Bueno *et al* ⁴² demonstrated that type II alveolar epithelial cells (AECII) from patients with IPF have accumulation of dysfunctional mitochondria and impaired mitophagy; this correlated with decreased levels of PINK1, and PINK1 silencing in normal lung epithelial cells resulted in a profibrotic phenotype. This study also demonstrated that mitochondrial dysfunction led to increased ER stress, vulnerability to AECII apoptosis and fibrosis. In a related study, Patel *et al* ⁴³ reported that PINK1 knockout mice are more susceptible to bleomycin-induced lung fibrosis. While these authors also found evidence of mitochondrial dysfunction in IPF lungs, they report increased levels of PINK1 in whole lung tissues from IPF lungs. Furthermore, this study demonstrated that these effects could be induced by TGF β -mediated increases in mtROS; scavenging of mtROS ameliorated these mitochondrial abnormalities.

Increased production of mtROS may contribute to mitochondrial dysfunction through other mechanisms. It was recently demonstrated that in bleomycin-induced pulmonary fibrosis in Wistar rats, there is acquisition of mtDNA deletions, respiratory chain dysfunction and mtROS production during the development of pulmonary fibrosis ⁴⁴. Similarly, Song *et al* ⁴⁵ demonstrated that inhibition of H₂O₂ or bleomycin-induced mtROS production by astaxanthin (AST) prevents AECII apoptosis, which may mitigate fibrotic responses.

There is a growing body of evidence linking mitochondrial dysfunction to the development of fibrosis. There is limited data on the role of mitochondrial dysfunction in the pathogenesis of SSc-associated fibrosis and other autoimmune diseases, and further research in this area is needed.

Impaired Autophagy

Autophagy is a cellular process whereby intrinsic damaged organelles/proteins or invading pathogens are targeted for lysosomal degradation (46). Autophagy is important in aging since an accumulation of damaged and dysfunctional organelles/proteins occurs during a cell's lifetime. Therefore, active and effective autophagy is needed for clearance of these abnormal proteins to maintain healthy cellular functions, and enhancing autophagy can promote delay cell aging (47). There is increasing evidence that defective autophagy might play a role in fibrosis associated with both IPF and autoimmune diseases (48–50).

Recent studies support a role for impaired autophagy in lung fibrosis. Cabrera *et al* ⁵¹ demonstrated that mice deficient in autophagin-1 protease (Atg4b-deficient mice) are more susceptible to bleomycin-induced lung fibrosis; in this study, deficient autophagy led to increased apoptosis of the alveolar and bronchiolar epithelial cells. In studies by Nho and Hergert ⁵², abnormalities in the autophagy pathway promoted a fibrotic phenotype of

lung fibroblasts when grown on type I collagen matrix. In comparison to normal lung fibroblasts, IPF fibroblasts had less autophagosomes, increased mTOR activity and decreased PTEN expression, thus preventing fibroblast apoptosis.

There is increasing evidence that autophagy is critical in the pathogenesis of SSc. When SSc skin biopsies were compared to healthy controls, SSc samples demonstrated increased autophagy early in the disease course, but decreased autophagy as the disease progressed *(53). Dumit *et al* *(54) demonstrated that the phenotype of SSc skin fibroblasts and fibroblasts from older patients share similarities; for example, both groups expressed minichromosome maintenance (MCM) helicase proteins to a lesser degree than young, normal skin fibroblasts. This study showed that decreased MCM7 is associated with reduced autophagy, decreased proliferation, and increased accumulation of intracellular proteins in both aged and SSc skin fibroblasts. These findings lend further support for the hypothesis that SSc exhibits an accelerated aging phenotype.

Conclusion

Recent studies provide evidence for aging phenotypes in SSc-associated fibrosis. Aging appears to influence the disease course and mortality in SSc patients, suggesting that aging contributes to disease progression; thus, SSc may be considered a disease process with an accelerated aging phenotype. We have reviewed current evidence for immune dysregulation, epigenetic modifications, cellular senescence, mitochondrial dysfunction and impaired autophagy in the pathogenesis of fibrosis and SSc. Understanding specific roles of these aging-related processes in the altered phenotypes of endothelial cells, immune cells and fibroblasts will provide new opportunities to treat the vasculopathy, inflammation and fibrosis that characterize SSc (Figure 1).

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Key Points

- Aging is associated with worse outcomes and increased mortality in SSc
- Cellular processes such as immune dysregulation, epigenetic modifications, senescence, mitochondrial dysfunction and impaired autophagy may contribute to the genesis and/or progression of inflammation and fibrosis associated with SSc
- Further studies are required to define specific roles of aging phenotypes/hallmarks in SSc-associated vasculopathy, inflammation and fibrosis.

Figure 1.

SSc-associated fibrosis, inflammation and vasculopathy may be perpetuated or accelerated by aging-associated phenotypes that include immune dysregulation, epigenetic modifications, cellular senescence, mitochondrial dysfunction and impaired autophagy. Immune dysfunction, specifically immune-senescence, may fail to clear the accumulation of senescent (myo)fibroblasts that acquire an apoptosis-resistant phenotype. The elaboration of pro-inflammatory cytokines, matrix metalloproteinases (MMPs) and reactive oxygen species (ROS) by the so-called senescence-associated secretory phenotype (SASP) of fibroblasts and immune cells promotes the apoptosis-susceptible phenotype of adjacent epithelial cells and endothelial cells, thus providing a feed-forward mechanism for aberrant tissue remodeling.