REVIEW

OPEN

Beyond fibrinolysis: the multifaceted role of the fibrinolytic system in systemic sclerosis

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Purpose of review
This review summarizes the emerging role of the fibrinolytic system in the pathogenesis of systemic sclerosis (SSc) and its potential as a source of novel therapeutic targets.

Recent findings
Increasing evidence indicates that SSc is characterized by impaired fibrinolysis, largely driven by upregulation of plasminogen activator inhibitor-1 (PAI-1) and α2-antiplasmin, which limits extracellular matrix degradation and promotes myofibroblast differentiation. A key pathogenic mechanism involves matrix metalloproteinase-12-mediated proteolytic cleavage of the urokinase-type plasminogen activator receptor (uPAR), which compromises angiogenesis and promotes endothelial-to-mesenchymal transition, thereby contributing to both vascular remodeling and fibrosis. Moreover, aberrant crosstalk between cleaved uPAR and N-formyl peptide receptors (FPRs) on fibroblasts induces excessive reactive oxygen species generation and sustained fibroblast proliferation. Clinically, circulating soluble uPAR and *PLAUR* gene polymorphisms have emerged as candidate biomarkers of severe microvascular dysfunction and internal organ involvement. From a therapeutic perspective, several innovative strategies, including uPAR-targeting peptides, PAI-1 inhibitors, and molecules disrupting uPAR-FPR interaction, have shown encouraging antifibrotic efficacy in preclinical models.

Summary
The fibrinolytic system has emerged as a central molecular hub linking SSc microvascular dysfunction, immune dysregulation, and fibrosis. Thus, restoring fibrinolytic homeostasis may offer a promising strategy to simultaneously improve angiogenesis, reduce fibrosis, and slow disease progression.

Keywords
fibrinolytic system, fibrosis, systemic sclerosis, therapeutic targets, vasculopathy

INTRODUCTION

Systemic sclerosis (SSc) is a chronic autoimmune connective tissue disease characterized by the interplay of microvascular injury, immune dysregulation, and progressive fibrosis affecting the skin and internal organs [1–3]. It represents the systemic autoimmune rheumatic disease with the highest mortality, mainly due to interstitial lung disease and pulmonary arterial hypertension [1,3,4].

Endothelial dysfunction is considered an early pathogenic event, preceding overt fibrosis and clinically manifesting as Raynaud's phenomenon [1,2,4]. Endothelial injury results in progressive capillary loss, defective angiogenesis, and an imbalance between vasodilatory and vasoconstrictive mediators [2,4]. Despite increased vascular endothelial growth factor (VEGF) expression, angiogenesis remains ineffective because of antiangiogenic factors and intrinsic endothelial abnormalities [4,5]. Concurrently, activation of innate and adaptive immunity promotes the production of profibrotic cytokines, including interleukin (IL)-6, IL-1β, and CCL2, sustaining chronic inflammation and tissue hypoxia [1,3,4]. These processes ultimately converge on persistent activation of myofibroblasts, mainly arising from resident fibroblasts and endothelial-to-mesenchymal transition (EndoMT), under the

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KEY POINTS

- The fibrinolytic system has emerged as a central molecular hub linking the three cardinal pathogenic processes of systemic sclerosis (SSc): microvascular damage, immune dysregulation, and progressive fibrosis.
- Proteolytic cleavage of the urokinase-type plasminogen activator receptor (uPAR) in endothelial cells represents a critical pathogenic event in SSc vasculopathy. By disrupting the receptor's proangiogenic activity and promoting endothelial-to-mesenchymal transition, this process drives the progression from microvascular injury to pathological tissue remodeling.
- A "fibrinolytic shutdown," driven by persistent upregulation of plasminogen activator inhibitor-1 and α2-antiplasmin, and aberrant crosstalk between cleaved uPAR and N-formyl peptide receptors in SSc fibroblasts sustain profibrotic myofibroblast activation, oxidative stress, and persistent cell proliferation.
- Circulating soluble uPAR and *PLAUR* gene polymorphisms have emerged as candidate biomarkers for disease stratification and the prediction of severe vasculopathy and internal organ involvement.
- Preclinical evidence suggests that therapeutic strategies aimed at restoring fibrinolytic homeostasis hold considerable promise as disease-modifying approaches for SSc.

predominant control of transforming growth factor-β (TGF-β), leading to excessive extracellular matrix (ECM) deposition and organ fibrosis [3,4,6].

Increasing evidence identifies the fibrinolytic system as a central regulator linking vascular injury with tissue remodeling in SSc [5]. This system is responsible for dissolving fibrin and maintaining vascular homeostasis through a finely regulated proteolytic cascade [5]. The central component is the proenzyme plasminogen, which is converted into the active serine protease plasmin by two primary activators: tissue-type plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA) [5]. While tPA is mainly synthesized by endothelial cells to regulate intravascular fibrinolysis, uPA binds to its specific receptor, uPAR (CD87), to focus proteolytic activity at the cell surface, thereby modulating cell adhesion, migration, and tissue remodeling [5]. Plasmin functions as a broad-spectrum protease that not only degrades fibrin and various ECM components (e.g., fibronectin and laminin), but also indirectly promotes matrix degradation and remodeling by activating matrix metalloproteinases (MMPs) and latent growth factors like TGF-β [5]. This system is strictly controlled by specific inhibitors, notably plasminogen activator inhibitor-1 (PAI-1), which blocks tPA and uPA, and α2-antiplasmin (α2AP), the primary inhibitor of plasmin [5]. In SSc, this balance appears to be profoundly disrupted: elevated levels of PAI-1 and α2AP contribute to a "fibrinolytic shutdown" that promotes fibrin deposition and myofibroblast differentiation [5]. Furthermore, the functional integrity of uPAR is compromised in SSc due to MMP-12-mediated cleavage, a process that impairs its ability to interact with integrins and sustain effective angiogenesis while promoting EndoMT [5]. Additionally, the proteolytic cleavage of plasminogen can generate angiostatin, a potent antiangiogenic factor that is found at increased levels in SSc patients and further contributes to defective vascular repair [5].

The purpose of this review is to summarize the complex pathogenic involvement of the fibrinolytic system in SSc and to discuss emerging therapeutic perspectives, highlighting how the various components of this proteolytic cascade, including activators, receptors, and inhibitors, may serve as novel molecular targets to counteract vascular dysfunction and progressive tissue fibrosis.

IMPLICATIONS OF THE FIBRINOLYTIC SYSTEM IN SYSTEMIC SCLEROSIS PATHOGENESIS

The fibrinolytic system has emerged as a critical molecular link connecting vasculopathy, fibrosis, and immune dysregulation in SSc [5,7].

Within the microvascular compartment, constitutive overexpression of MMP-12 by endothelial cells and dermal fibroblasts induces proteolytic cleavage of uPAR through the removal of its N-terminal D1 domain, generating a truncated D2+D3 receptor that loses its ability to support endothelial migration and angiogenesis (Fig. 1) [8–10]. Cleavage of uPAR disrupts its interaction with β2 integrins and the actin cytoskeleton, while MMP-12 simultaneously promotes angiostatin generation through plasminogen cleavage, creating a persistently antiangiogenic environment despite elevated VEGF levels (Fig. 1) [8–10]. Recent evidence has identified metabolic alterations as a key driver of this cascade [11]. SSc dermal fibroblasts undergo a marked metabolic shift toward aerobic glycolysis, characterized by increased lactate production and progressive acidification of the extracellular milieu [11,12]. This acidic microenvironment directly triggers the upregulation of MMP-12 in endothelial cells, leading to accelerated uPAR proteolytic cleavage and functional inactivation [11]. Furthermore, the disruption of the uPA/uPAR axis induced by this glycolysis-derived acidity has been reported as a primary driver of the EndoMT

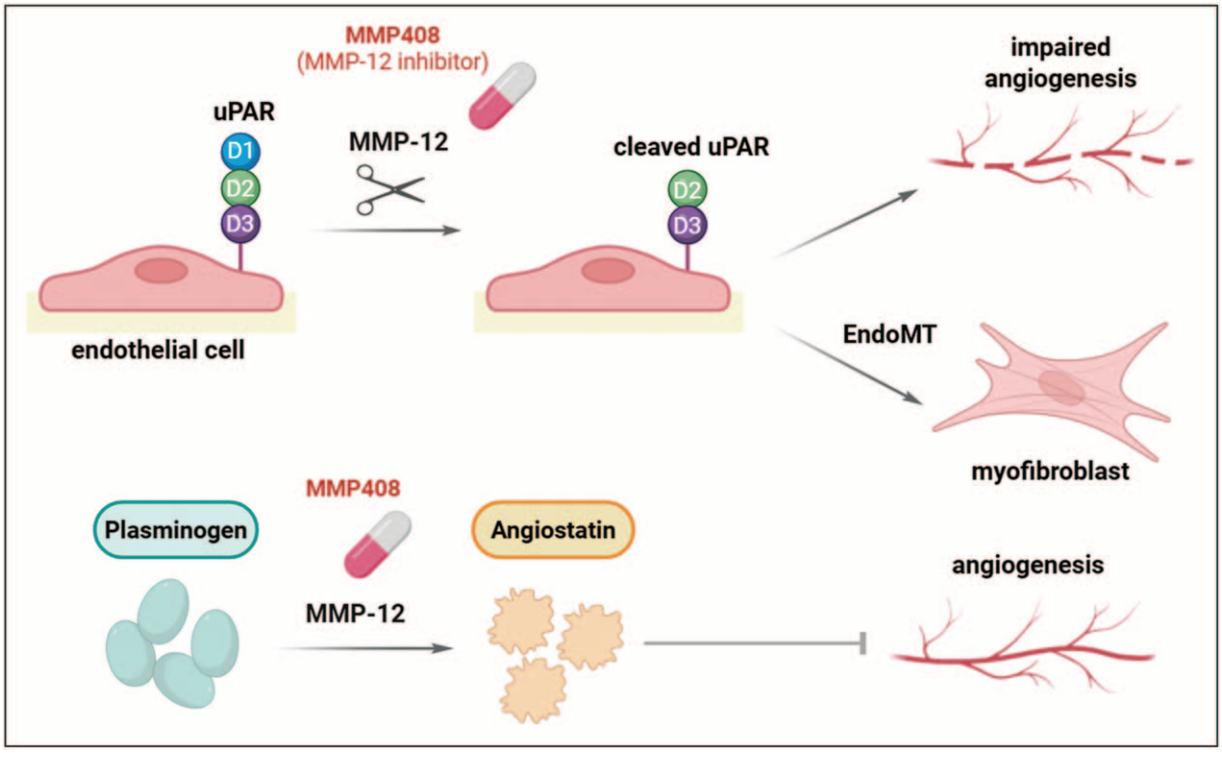

FIGURE 1. MMP-12-mediated uPAR cleavage and microvascular dysfunction in SSc. MMP-12-mediated proteolytic cleavage of uPAR in SSc microvascular endothelial cells leads to the loss of the N-terminal D1 domain, resulting in defective angiogenesis and the induction of EndoMT. In parallel, MMP-12 cleaves plasminogen to generate high levels of angiostatin, which further suppresses vascular repair and growth. Selective inhibition of MMP-12 (e.g., with MMP408) represents a promising therapeutic strategy to improve the angiogenic response and inhibit EndoMT-driven fibrosis. EndoMT, endothelial-to-mesenchymal transition; MMP-12, matrix metalloproteinase-12; SSc, systemic sclerosis; uPAR, urokinase-type plasminogen activator receptor.

process, providing an essential pathogenic link between metabolic reprogramming, microvascular injury, and progressive tissue fibrosis [11,12]. Consistently, exposure of healthy endothelial cells to MMP-12-rich SSc serum induces EndoMT, whereas pharmacological inhibition of MMP-12 prevents this process, confirming the pathogenic relevance of uPAR cleavage (Fig. 1) [13]. Moreover, endothelial dysfunction is further aggravated by increased PAI-1 and α2AP levels, which promote endothelial senescence and interfere with VEGF signaling [14,15▪]. Similar mechanisms contribute to cardiac vascular remodeling associated with uPAR deficiency, which was found to trigger a significant depletion of endothelial cells and to promote EndoMT [16▪].

Beyond vascular injury, the fibrinolytic system directly regulates fibroblast activation [7,15▪]. During TGF-β-induced myofibroblast differentiation, full-length uPAR is cleaved on the fibroblast surface, disrupting its interaction with integrins and enhancing cell adhesion, cytoskeletal tension, α-smooth muscle actin (α-SMA) incorporation into stress fibers, and ECM production (Fig. 2) [17]. Preventing uPAR cleavage pharmacologically or by expressing non-cleavable uPAR abolishes myofibroblast differentiation, identifying this event as a key molecular checkpoint of fibrosis [17].

The profibrotic activity of the fibrinolytic system is further sustained by aberrant crosstalk between cleaved uPAR and N-formyl peptide receptors (FPRs) [18,19▪,20]. SSc fibroblasts overexpress FPR1, FPR2, and FPR3 together with cleaved uPAR, promoting myofibroblast differentiation and increased expression of α-SMA, vitronectin, αvβ5 integrin, collagen, and fibronectin (Fig. 3) [18]. Mechanistically, uPAR cleavage exposes the SRSRY sequence, enabling formation of an FPR/uPAR/integrin signaling complex that activates Rac1, ERK1/2, and the NADPH oxidase (NOX2) complex, resulting in excessive reactive oxygen species (ROS) generation and persistent profibrotic gene expression (Fig. 3) [18,19▪,20]. The same pathway also promotes fibroblast proliferation through c-Myc and Cyclin D1 activation, whereas pharmacological disruption of the FPR/uPAR interaction attenuates both oxidative stress and fibroblast expansion (Fig. 3) [19▪,20].

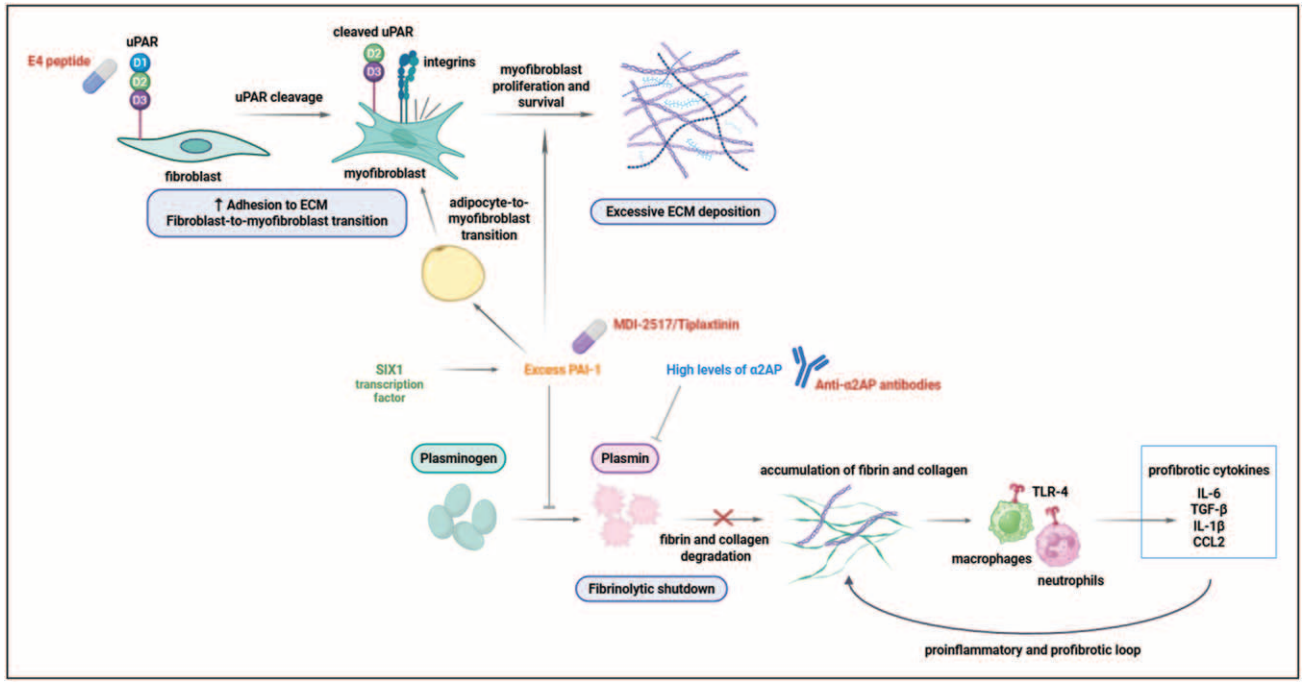

FIGURE 2. Fibroblast activation, adipocyte-to-myofibroblast transition, and the proinflammatory/profibrotic "fibrinolytic shutdown" loop in SSc. Proteolytic cleavage of uPAR in fibroblasts, characterized by the loss of the D1 domain, serves as a primary driver of their differentiation into contractile myofibroblasts. The SSc profibrotic environment is further sustained by a "fibrinolytic shutdown" caused by an excess of PAI-1 (driven by the transcription factor SIX1) and α2AP. Specifically, elevated PAI-1 levels reinforce myofibroblast proliferation and survival while simultaneously promoting the adipocyte-to-myofibroblast transition, leading to the progressive loss of dermal white adipose tissue. Additionally, the resulting accumulation of undegraded fibrin acts as a proinflammatory ligand for TLR-4 on recruited macrophages and neutrophils; these cells, in turn, secrete profibrotic cytokines that establish a self-perpetuating proinflammatory and profibrotic loop. Therapeutic strategies include the E4 peptide to restore protective uPAR-dependent signaling, PAI-1 inhibitors *(e.g.*, MDI-2517 and Tiplaxtinin), and neutralizing antibodies against α2AP to counteract the "fibrinolytic shutdown" and mitigate progressive tissue fibrosis. α2AP, α2-antiplasmin; PAI-1, plasminogen activator inhibitor-1; SSc, systemic sclerosis; TLR-4, Toll-like receptor-4; uPAR, urokinase-type plasminogen activator receptor.

Alterations in fibrinolytic components differ among SSc subsets [21]. Fibroblasts from limited cutaneous SSc display increased uPA and PAI-1 expression, suggesting that elevated PAI-1 predominates over uPA activity and favors ECM accumulation [21]. Conversely, although lesional skin from diffuse cutaneous SSc is characterized by impaired fibrinolytic activity promoting fibrosis, clinically unaffected areas exhibit increased uPAR expression, potentially preserving local fibrinolytic activity before overt fibrosis develops [21].

A growing body of evidence indicates that the profibrotic microenvironment in SSc is further reinforced by a state of "fibrinolytic shutdown" characterized by a sustained upregulation of PAI-1 (Fig. 2), which not only impairs ECM degradation by inhibiting plasmin generation, but also suppresses the protective uPA/uPAR/PPARγ/Smad7 signaling axis, which normally acts as a molecular brake on TGF-β-driven fibrogenesis [15▪,22]. Accordingly, *uPAR* gene silencing enhances fibroblast proliferation, migration, contractility, and collagen synthesis, whereas *PAI-1* knockdown exerts the opposite effects [22]. In bleomycin-induced skin fibrosis, pharmacological inhibition of PAI-1 reduces dermal thickening and collagen deposition, whereas uPAR inhibition aggravates fibrosis [22]. Recent evidence demonstrated that the molecular regulation of the "fibrinolytic shutdown" and PAI-1-mediated profibrotic program involves the transcription factor SIX1, whose expression in SSc skin significantly correlates with disease severity [23▪▪]. Indeed, SIX1 directly activates the PAI-1 encoding gene (*SERPINE1*) promoter and drives PAI-1 overexpression (Fig. 2) [23▪▪]. Of note, SIX1-mediated upregulation of PAI-1 not only strengthens the myofibroblast phenotype, but also promotes the adipocyte-to-myofibroblast transition, a process that contributes to the progressive

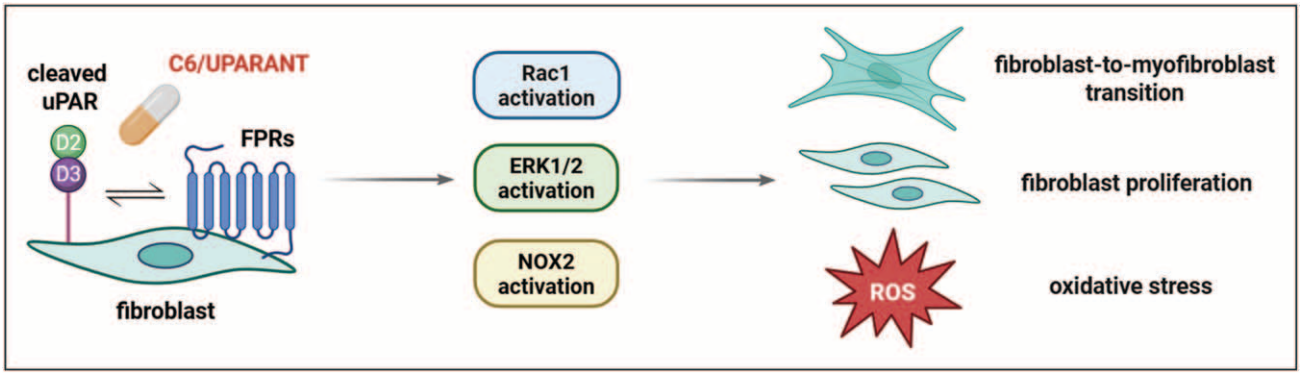

FIGURE 3. Profibrotic uPAR/FPR crosstalk in SSc fibroblasts. Cleaved uPAR on SSc fibroblast surface establishes an aberrant crosstalk with FPRs, leading to increased ROS production and persistent cell proliferation. This interaction drives a signaling cascade (involving Rac1, ERK1/2, and the NOX2 complex) that sustains the activated myofibroblast phenotype and the relentless progression of tissue fibrosis. Targeting this signaling axis with molecules that disrupt the uPAR/FPR interaction (e.g., C6 or UPARANT) offers a novel disease-modifying approach to attenuate fibroblast activation and halt fibrotic progression. FPR, N-formyl peptide receptor; ROS, reactive oxygen species; SSc, systemic sclerosis; uPAR, urokinase-type plasminogen activator receptor.

loss of dermal white adipose tissue characteristic of SSc (Fig. 2) [23▪▪]. Mechanistically, SIX1 also enhances the bioavailability of latent TGF-β through the regulation of latent TGF-β-binding protein 4 (LTBP4), which further sustains the profibrotic niche [23▪▪]. Moreover, *in vivo* studies have demonstrated that adipocyte-specific deletion of the *SIX1* gene effectively preserves dermal white adipose tissue integrity and attenuates collagen deposition and dermal thickening in experimental SSc, suggesting that targeting the SIX1/PAI-1 axis could represent a novel antifibrotic therapeutic strategy [23▪▪].

Another hallmark of "fibrinolytic shutdown" in SSc is increased α2AP (Fig. 2), which enhances TGF-β and prostaglandin F2α production, thereby reinforcing skin fibroblast activation, myofibroblast persistence, and ECM accumulation [14,24,25].

Beyond the skin, dysregulation of the fibrinolytic system contributes to multiorgan fibrosis, such as pulmonary, pleural, and cardiac fibrosis [16▪,26,27,28]. In the lung, vascular leakage promotes fibrin deposition that serves as a scaffold for fibroblast migration, while uPA/uPAR signaling coordinates integrins and protease-activated receptor-1 to regulate migration, differentiation, and cytokine production [27]. Although plasmin activity is reduced in the alveolar compartment, local interstitial plasmin promotes fibrosis through MMP activation and TGF-β release [27]. PAI-1 further amplifies pulmonary fibrosis by inhibiting fibrinolysis and sensitizing epithelial cells to apoptosis [27]. Reduced uPAR expression in airway epithelial cells and macrophages exacerbates pulmonary fibrosis by increasing IL-6 production, epithelial-to-mesenchymal transition, and tissue remodeling, whereas plasminogen administration restores fibrinolytic activity and promotes fibrosis resolution in experimental models [28]. In the pleura, uPA/uPAR signaling regulates mesothelial-to-mesenchymal transition, while in the heart *uPAR* gene deficiency enhances TGF-β1 signaling, ECM deposition, and perivascular fibrosis [16▪,26]. In particular, by employing 3D cardiospheres generated from nonmyocyte cardiac cells of *uPAR*-knockout mice, it has been demonstrated that the absence of uPAR led to an overproduction of active TGF-β1 and the potentiation of its profibrotic activity *via* the activation of the noncanonical Akt signaling pathway [16▪]. Mechanistically, this molecular shift drives excessive ECM synthesis and increased tissue stiffness, while simultaneously impairing integrin-dependent cell-matrix interactions [16▪].

In addition to fibrosis, the fibrinolytic system modulates immune responses. Cleaved uPAR/FPR signaling sustains ROS production and inflammatory pathways in fibroblasts [18,19▪,20], whereas reduced uPAR expression in macrophages enhances IL-6 production and promotes a profibrotic inflammatory phenotype [28]. Moreover, impaired fibrinolysis results in fibrin accumulation, which activates Toll-like receptor-4 on macrophages and neutrophils, perpetuating chronic inflammation and fibrosis (Fig. 2) [7].

MODELING FIBRINOLYTIC SYSTEM DYSFUNCTION IN VIVO

Experimental models targeting the fibrinolytic system have provided compelling evidence for its central role

in SSc pathogenesis [7,15▪]. Among them, the *uPAR*-knockout mouse is particularly relevant because it spontaneously reproduces the three cardinal features of SSc, namely microvasculopathy, chronic inflammation, and progressive fibrosis [29]. Loss of uPAR results in severe dermal fibrosis characterized by increased skin thickness, collagen accumulation, replacement of subcutaneous adipose tissue by connective tissue, and marked myofibroblast expansion [29,30]. These changes are accompanied by endothelial apoptosis and capillary rarefaction, confirming the essential role of uPAR in vascular homeostasis [29]. *uPAR*-knockout mice also develop progressive pulmonary fibrosis resembling human nonspecific interstitial pneumonia and exhibit cardiac alterations closely reproducing SSc cardiomyopathy, including ischemic lesions, cardiomyocyte hypertrophy, endothelial loss, reduced capillary density, and extensive myocardial fibrosis [29,31]. Mechanistically, *uPAR* deficiency promotes EndoMT through enhanced TGF-β1 signaling, impaired uPA internalization, increased extracellular uPA accumulation, and altered integrin-dependent cell-matrix interactions, ultimately favoring persistent myofibroblast activation and ECM deposition [32]. The observation that uPAR expression is reduced in SSc skin and myocardium further supports the translational relevance of this model [29,31]. Accordingly, the *uPAR*-knockout mouse represents a valuable platform for investigating disease mechanisms and testing antifibrotic therapies [33]. The protective role of uPAR is further highlighted by mesenchymal stem/stromal cell (MSC) studies [33]. Indeed, wild-type MSCs attenuate bleomycin-induced pulmonary fibrosis, whereas *uPAR*-deficient MSCs display markedly reduced therapeutic efficacy owing to impaired expression of uPA, MMP-2, and MMP-9 and defective activation of plasmin-dependent fibrinolysis [33]. However, the contribution of uPAR to renal fibrosis appears context dependent, as its deficiency aggravates obstructive nephropathy while protecting against lipopolysaccharide-induced glomerulosclerosis [7]. Likewise, the uPAR-targeting peptide UPARANT, which inhibits uPAR interaction with FPRs, ameliorates experimental diabetic nephropathy by suppressing inflammatory signaling [7].

In contrast, studies on PAI-1 have revealed tissue-specific effects. In the lung, PAI-1 consistently acts as a profibrotic mediator, since its overexpression worsens bleomycin-induced fibrosis whereas genetic deletion attenuates collagen accumulation [15▪,34]. Nevertheless, selective deletion of *PAI-1* gene in myeloid cells unexpectedly exacerbates pulmonary fibrosis, indicating that PAI-1 also restrains excessive macrophage invasiveness and proteolytic activity [35]. In the skin, however, *PAI-1* deficiency fails to prevent bleomycin-induced fibrosis, suggesting that dermal fibrogenesis can proceed through compensatory pathways independent of canonical fibrinolytic inhibition [34]. Moreover, aged *PAI-1*-knockout mice spontaneously develop cardiac fibrosis and enhanced susceptibility to EndoMT, emphasizing the context-dependent biological functions of PAI-1 [15▪].

Beyond uPAR and PAI-1, studies in genetically modified mice revealed that other fibrinolytic components also contribute to tissue remodeling [7]. In particular, tPA supports myofibroblast survival through lipoprotein-related protein-1 signaling, whereas both pharmacological inhibition and genetic deletion of α2AP consistently reduce dermal and renal fibrosis, improve vascular function, and decrease autoantibody production in experimental SSc [7,25].

FIBRINOLYTIC SYSTEM AS A SOURCE OF DIAGNOSTIC AND PROGNOSTIC BIOMARKERS

Several components of the fibrinolytic system have emerged as promising biomarkers of disease severity and organ involvement in SSc [36–40]. Among them, soluble uPAR (suPAR) is the most extensively investigated. Circulating suPAR levels are significantly increased in SSc, particularly in the diffuse cutaneous disease, and correlate with anti-Scl70 autoantibody positivity, advanced microvascular damage, interstitial lung disease, pulmonary arterial hypertension, digital ulcers, and impaired pulmonary function [36,38]. The suPARnostic ELISA appears to provide greater diagnostic accuracy than conventional assays [38].

Genetic variability within the gene encoding uPAR (*PLAUR*) also carries prognostic value [37]. Particularly, the *PLAUR* gene promoter polymorphism rs344781 has been found to be independently associated with an increased risk of digital ulcers and pulmonary arterial hypertension, identifying patients more prone to severe vascular complications [37].

Consistent with impaired fibrinolysis, SSc patients exhibit reduced circulating uPA and increased PAI-1 levels [38]. Serum PAI-1 correlates positively with TGF-β isoforms and VEGF-A, supporting its role as a biomarker of active fibrogenesis and vascular dysfunction [38,39]. Although associations between *SERPINE1* gene polymorphisms and disease susceptibility remain inconsistent among different populations, elevated circulating PAI-1 is a reproducible feature of SSc and reflects vasculopathy, cellular senescence, and progressive fibrosis [15▪,38,39]. Additional fibrinolytic cascade-related biomarkers include increased plasma tPA, reduced D-dimer

concentrations, and elevated dermatan sulfate, the latter inversely correlating with forced vital capacity and potentially reflecting pulmonary involvement [40].

Overall, fibrinolytic biomarkers may improve patient stratification, facilitate early identification of severe vascular and pulmonary complications, and support prognostic assessment in SSc.

HARNESSING THE FIBRINOLYTIC SYSTEM FOR THERAPEUTIC INTERVENTION

Given its central role in vascular dysfunction and fibrosis, the fibrinolytic system represents an attractive therapeutic target in SSc and other fibrotic disorders [7,14,15▪,41].

Among the most promising approaches, the endostatin-derived peptide E4 restores fibrinolytic balance by binding uPAR and activating the uPA pathway [41]. In human SSc lung cultures, E4 increases the uPA/PAI-1 ratio, enhances MMP-1 and MMP-3 expression, promotes collagen and fibronectin degradation, and markedly reduces established fibrosis [41]. These effects are completely abolished by uPAR silencing or genetic deletion, demonstrating their strict dependence on the uPA/uPAR axis [41]. Restoration of uPA activity has shown similar benefits in experimental fibrosis [7,42,43]. Lung-specific uPA overexpression prevents bleomycin-induced collagen accumulation, reduces tissue stiffness, and accelerates resolution of established fibrosis by promoting myofibroblast apoptosis [7,42]. Likewise, transplantation of *uPA* gene-modified liver stem cells attenuates experimental hepatic fibrosis by inhibiting myofibroblast activation [7,43]. Conversely, inhibition of the uPA/uPAR pathway aggravates fibrosis. In bleomycin-induced skin fibrosis, pharmacological uPAR inhibition with amiloride worsens dermal fibrosis, whereas uPAR agonists or PAI-1 inhibition with Tiplaxtinin significantly reduce dermal thickening and collagen deposition [22].

Among PAI-1 inhibitors, the novel small molecule MDI-2517 has recently shown potent antifibrotic activity, suppressing profibrotic gene expression in SSc fibroblasts and reducing both dermal and pulmonary fibrosis more effectively than standard therapies in preclinical models [15▪,44▪▪]. Hence, these findings identify MDI-2517 as a promising first-in-class therapeutic candidate to halt the progressive multiorgan remodeling that characterizes SSc [15▪,44▪▪].

Another promising strategy targets the interaction between cleaved uPAR and FPRs [19▪]. The synthetic compound C6, designed to disrupt this interaction, effectively inhibits the abnormal proliferative phenotype of SSc fibroblasts, supporting the FPR/uPAR signaling complex as a potential disease-modifying target [19▪]. Similarly, selective inhibition of MMP-12 with compounds such as MMP408 prevents pathological uPAR cleavage, preserves endothelial function, and limits EndoMT, suggesting a dual therapeutic effect on vascular injury and fibrosis [13].

Finally, increasing attention has focused on α2AP [14]. Neutralizing antibodies against α2AP reduce fibrosis and improve vascular function in experimental SSc, while microplasmin neutralizes circulating α2AP activity and enhances fibrinolysis [14]. Additional approaches include restoration of MMP-3 activity, inhibition of antiplasmin-cleaving enzymes or dipeptidyl peptidase-4, and suppression of α2AP expression through microRNAs such as miR-30c, all of which reduce myofibroblast activation and ECM accumulation in preclinical models [14].

Collectively, these findings support therapeutic restoration of fibrinolytic homeostasis as a promising disease-modifying strategy capable of simultaneously targeting vascular dysfunction and progressive fibrosis in SSc.

CONCLUSION

The fibrinolytic system has emerged as a central molecular hub linking the three major pathogenic processes of SSc: vasculopathy, immune dysregulation, and fibrosis. MMP-12-mediated uPAR cleavage impairs angiogenesis and promotes EndoMT, while aberrant FPR/uPAR signaling in fibroblasts sustains myofibroblast activation through oxidative stress and uncontrolled proliferation (Figs. 1 and 3). Simultaneously, persistent upregulation of PAI-1 and α2AP establishes a state of "fibrinolytic shutdown," suppressing ECM degradation while amplifying TGF-β-dependent profibrotic signaling (Fig. 2). Beyond their pathogenic role, fibrinolytic components have considerable clinical relevance. Circulating suPAR and PAI-1, as well as *PLAUR* genetic variants, represent promising biomarkers for disease stratification, vascular complications, and internal organ involvement. Experimental evidence further indicates that restoring fibrinolytic homeostasis through enhancement of uPA/uPAR signaling, inhibition of MMP-12, blockade of the uPAR/FPR interaction, or targeting PAI-1 and α2AP can effectively attenuate fibrosis and improve vascular function (Figs. 1–3). Although these strategies remain largely preclinical, they identify the fibrinolytic system as one of the most promising sources of future disease-modifying therapies for SSc. Further studies are required to define the molecular mechanisms governing fibrinolytic dysregulation

and to translate these findings into targeted clinical interventions capable of simultaneously restoring angiogenesis and limiting progressive multiorgan fibrosis.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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This pivotal study introduces MDI-2517 as a first-in-class, small-molecule PAI-1 inhibitor with potent disease-modifying properties. Since MDI-2517 suppresses profibrotic gene expression in SSc fibroblasts and demonstrates superior efficacy over standard treatments in attenuating both dermal and pulmonary fibrosis in vivo, this work identifies PAI-1 inhibition as a highly promising strategy to halt progressive multiorgan remodeling.