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Are tyrosine kinase inhibitors promising for the treatment of systemic sclerosis and other fibrotic diseases?

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Summary

Tissue fibrosis causes organ failure and death in patients with systemic sclerosis (SSc), but clearly effective anti-fibrotic therapies are not available. The tyrosine kinase inhibitor (TKI) imatinib, which blocks the pro-fibrotic c-Abl kinase and PDGF receptor, is currently evaluated in clinical proof-of-concept trials for the treatment of patients with SSc. In experimental models, imatinib efficiently prevented and reduced tissue fibrosis. First clinical case studies demonstrated anti-fibrotic effects of imatinib in selected patients with SSc and other fibrotic diseases, and observational studies in sclerotic chronic graft-versus-host disease showed promising results. Besides imatinib, the two novel TKIs of c-Abl and PDGF receptor nilotinib and dasatinib have recently proven efficacy in experimental models of SSc. The potential of TKIs of the VEGF receptor (e.g., semaxinib, vatalanib, sutent, and sorafenib) and the EGF receptor (e.g., erlotinib, gefitinib, lapatinib, and canertinib) as anti-fibrotic treatments are also discussed in this review. Prior to clinical use, however, controlled trials need to address efficacy as well as tolerability of TKIs in patients with different fibrotic diseases.

Key words: systemic sclerosis, fibrosis, tyrosine kinase inhibitors

Introduction

Systemic sclerosis (SSc) is a connective tissue disease characterised by progressive fibrosis of the skin and internal organs, including the lungs, gut, and heart. Although its aetiology remains unknown, knowledge about the pathogenesis of SSc is steadily increasing. Three pathologic hallmarks characterise the development of SSc: autoimmunity, vasculopathy, and progressive tissue fibrosis. While inflammatory, autoimmune processes and vasculopathy with capillary rarification dominate early stages of SSc, progressive tissue fibrosis is the key feature of late-stage disease. Progressive tissue fibrosis can cause organ failure and accounts for much of the morbidity and mortality in patients with SSc [1]. Consequently, SSc research aims for novel treatment strategies to either prevent or reduce tissue fibrosis.

Tyrosine kinases (TKs) regulate a wide variety of normal cell processes, including metabolism, growth, differentiation, and apoptosis. Phosphorylation of target proteins at tyrosine residues is the common mode of action of TKs. According to their localisation in the cell, TKs can be classified in two major groups: The receptor TKs are membrane receptors that activate intracellular signaling pathways upon ligand binding to their extracellular domains. This process includes the dimerisation of two TK monomers as well as autophosphorylation of the intracellular phosphatase domain to increase the catalytic activity. In contrast, non-receptor TKs lack extracellular and transmembrane domains but modulate signaling pathways after activation in the cytoplasm [2].

Besides their physiological roles, TKs are key players of various diseases, including cancer, pulmonary arterial hypertension, and systemic sclerosis (SSc). In this context, pathological activation of TKs may drive carcinogenesis, vascular remodelling, and fibrogenesis [3–5]. To target pathological TK activity, researchers are developing monoclonal antibodies against the extracellular domains of receptor TKs, such as the anti-vascular endothelial growth factor (VEGF) receptor antibody bevacizumab and the anti-epithelial growth factor (EGF) receptor antibody cetuximab. In addition to monoclonal antibodies, small molecule tyrosine kinase inhibitors (TKIs), which can enter the cytoplasm to bind the intracellular catalytic domains of both receptor and non-receptor TKs, are emerging as novel therapies for targeting pathological TK activity in various diseases.

In this review, we will highlight the role of imatinib, a dual inhibitor of Abelson kinase (c-Abl) and platelet derived growth factor (PDGF) receptor, as a novel anti-fibrotic therapy in SSc and other fibrotic diseases. Furthermore, we will discuss chances and risks of VEGF and EGF receptor TKIs in the treatment of SSc.

First generation c-abl and PDGF receptor inhibitor imatinib

Imatinib was the first TKI to be established in the treatment of chronic myelogenous leukaemia (CML). Imatinib efficiently blocks the tyrosine kinase activity of the c-Abl, a non-receptor TK which is pathologically activated in CML. In addition to its role in cell proliferation, c-Abl can promote fibrosis as an important downstream target of tumour growth factor-β (TGF-β) [6]. TGF-β is one of the central mediators in pro-fibrotic diseases. In this context, the induction of extracellular matrix proteins by TGF-β is strongly decreased in cells deficient for c-Abl. In addition to its interaction with TGF-β, imatinib suppresses the TK activity of the PDGF receptor, which can also stimulate fibrogenesis and enhance fibroblast contractility via syndecan 4 and MEK/ERK-signaling [7]. Thus, imatinib targets simultaneously two major pro-fibrotic pathways in SSc (fig. 1), blocks the production of extracellular matrix, and reduces the contractility of fibroblasts [7, 8].

We demonstrated that imatinib in pharmacologically relevant concentrations inhibited the synthesis of collagen 1a1, collagen 1a2, and fibronectin-1 in SSc fibroblasts by up to 90% [9]. We did not observe any compensatory changes in the expression of matrix metalloproteinases and tissue inhibitors of matrix metalloproteinases. *In vivo* experiments confirmed these results as imatinib efficiently inhibited the development of bleomycin-induced dermal fibrosis in mice. Treatment of mice with imatinib at doses of 50 mg/kg/day and 150 mg/kg/day had strong anti-fibrotic effects. Imatinib prevented the differentiation of resting fibroblasts into myofibroblasts and reduced synthesis and accumulation of extracellular matrix in lesional skin. Finally, we found that imatinib did not only prevent the development of fibrosis but also reduced established fibrosis in experimental models of SSc [10]. Apart from SSc, imatinib exerted potent anti-fibrotic effects in experimental models of pulmonary, renal and liver fibrosis [6, 11–13]. Along with inhibition of pathological fibrosis in various diseases, imatinib can also block physiological wound healing by interfering with recruitment, proliferation, and functional activities of fibroblasts and pericytes [14].

Imatinib is widely used for the treatment of bcr-Abl-positive CML and gastrointestinal stromal tumours, and more than 100000 patients have been treated so far. Imatinib possesses favourable pharmacokinetics: It is readily absorbed after oral administration and it can be administered once daily due to its long half-life [8]. Imatinib is well tolerated and severe adverse effects are rare. Minor and moderate side-effects, however, are common and lead to discontinuation of the drug in 15–30% of the patients [15]. The adverse events of imatinib are dose-dependent and include oedema, muscle cramps, diarrhoea, and bone marrow toxicity [15, 16]. Imatinib and other inhibitors of c-Abl and PDGF receptor might also slightly increase the risk of congestive heart failure, especially in patients with a previous history of heart disease [17, 18]. This could be of relevance for treatment of SSc, as subclinical microvascular and fibrotic changes of the myocardium are frequently seen in SSc patients.

Of note, smaller clinical case series in the treatment of CML confirmed the anti-fibrotic effects of imatinib in experimental models of fibrosis. In these case series, treatment with imatinib led to a regression of concomitant bone marrow fibrosis [19, 20]. Interestingly, the anti-fibrotic effect did not correlate with the cytogenetic response and thus, mechanisms independent from the suppression of Philadelphia chromosome-positive cancer cells might have caused regression of bone marrow fibrosis [20].

The anti-fibrotic effects of imatinib in experimental models of fibrosis and in the bone marrow of patients with CML as well as the good clinical safety profile in CML prompted the off-label use of imatinib in selected patients with severe or refractory fibrotic diseases. In this context, imatinib was an efficient therapy in two patients with gadolinium-induced nephrogenic systemic fibrosis [21]. Notably, the disease improved under imatinib, and worsened after stopping imatinib. Furthermore, several case studies demonstrated beneficial effects of imatinib in patients with refractory SSc [22–24]. As shown recently, imatinib appears to be highly effective in patients with refractory sclerotic chronic graft-versus-host disease (cGVHD) that shares several pathological features with SSc, including progressive skin fibrosis [25, 26]. Finally, we reported the successful treatment of pulmonary fibrosis with imatinib in a patient with mixed connective tissue disease [27]. Before initiation of imatinib, the patient rapidly deteriorated despite treatment with corticosteroids and methotrexate. When treated with imatinib at a dose of 400 mg/day over 20 weeks, the patient progressively improved. The New York Heart Association (NYHA) class changed from NYHA 4 to NYHA 2. The 6-min walking distance increased by 50 m and the predicted DL_{CO} increased from 26% to 45%. Moreover, the arterial oxygen pressure increased from 64 mm Hg to 70 mm Hg at rest and from 50 mm Hg to 62 mm Hg after exertion. Ground glass opacities decreased during treatment whereas reticular changes remained constant. Nevertheless, no changes in forced vital capacity and total lung capacity were observed. The patient tolerated the treatment well and did not experience any adverse events.

The promising results from small case studies with imatinib led to the initiation of clinical trials in patients with SSc. Since potent anti-fibrotic agents for the treatment of SSc do not exist yet, the results from these proof-of-concept trials are urgently awaited. If they give positive signals, larger placebo-controlled trials will be initiated. Nevertheless, the good results from the above-mentioned case studies should not be over-estimated: The course of SSc is variable with spontaneous regression of dermal fibrosis. Therefore, regression of fibrosis in these case reports might reflect the spontaneous course of the disease in individual patients but not a response to imatinib.

Second generation c-Abl and PDGF receptor inhibitors and Src inhibitors

Dasatinib and nilotinib, two novel inhibitors of c-abl and PDGF receptor, serve as salvage therapies for the treatment of refractory CML as well as for patients with intolerance to imatinib [28]. Similar to imatinib, dasatinib and nilotinib also inhibited the development of fibrosis in experimental models of SSc and might be interesting alternatives in the anti-fibrotic treatment with TKIs. Nilotinib and other TKIs of c-Abl and PDGF receptor might have positive effects on the proliferative vasculopathy of SSc besides their anti-fibrotic potential [29].

In addition to its direct effects on c-abl and the PDGF receptor, dasatinib inhibits Src kinases (fig. 1). These non-receptor TKs regulate the activation of c-abl. Src kinases are activated by pro-fibrotic cytokines, such as TGF-β and PDGF [30]. There is also evidence that Src kinases are critical for inflammatory responses [31]. In experimental models of SSc, the specific inhibitor of Src kinases SU6656 reduced the development of dermal fibrosis. Thus, targeting Src kinases may be another promising approach in the treatment of SSc [30]. Although selective inhibitors of Src kinases are not yet in clinical use, dasatinib inhibits Src kinases in pharmacologically relevant concentrations. A clinical proof-of-concept study with dasatinib in patients with SSc is ongoing.

TKIs of the VEGF receptor

Vascular endothelial growth factor (VEGF) is the primary inducer and key mediator of angiogenesis. Despite disturbed vessel morphology and severe capillary rarification, we found strong up-regulation of VEGF levels and VEGF receptors in the skin of patients with SSc [32]. We concluded that VEGF-driven, angiogenic processes might be futile and even deleterious in patients with SSc. In line with our results, several studies showed that sufficient tissue angiogenesis depends on strict regulation of VEGF expression. In contrast, chronic and uncontrolled over-expression of VEGF induced the formation of chaotic vessels, characterised by glomeruloid and haemangioma-like morphology similar to capillary changes seen in SSc [33–35].

Vasculopathy with capillary rarification as well as uncontrolled over-expression of VEGF and VEGF receptors may have further implications on the pathogenesis of SSc [36]. In patients with SSc, vascular rarification causes decreased blood flow and hypoxia in affected tissues. Severe tissue hypoxia may contribute to the development of tissue fibrosis by the induction of extracellular matrix proteins, including fibronectin-1, thrombospondin-1, proα2(I) collagen, IGF-binding protein 3 and TGF-β-induced protein [37]. Furthermore, there is recent evidence from transgenic mouse models that VEGF signaling itself can stimulate the production of extracellular matrix proteins [38], providing a potential molecular link between vascular changes and fibrosis in SSc (fig. 1).

Taken together, these findings might suggest beneficial effects of inhibition of VEGF signalling in patients with SSc by novel TKIs, such as semaxinib, vatalanib, sutent, and sorafenib. We believe, however, that the clinical use of VEGF receptor TKIs harbors potential risks: Complete inhibition of VEGF signalling by TKIs in patients with SSc might have more deleterious effects than over-stimulation of the VEGF/VEGF receptor axis. Thus, application of VEGF receptor TKIs could even worsen vasculopathy in patients with SSc and could prevent angiogenesis, which is desperately needed for wound healing in SSc patients with ulcers. Since it remains unknown how to achieve controlled expression and timely termination of VEGF signalling, which seems to be crucial for success of pro-angiogenic therapies, we discourage clinical use of VEGF receptor TKIs in patients with SSc at this time. Instead, we recommend careful evaluation of these drugs in experimental models of SSc prior to clinical application.

EGF receptor inhibitors

In cancer therapy, TKIs of the EGF receptor are emerging as important anti-neoplastic drugs to selectively target cancer cells with uncontrolled EGF signalling. The EGF receptor, a receptor tyrosine kinase, can promote tumour growth by activating central pathways of cell proliferation and survival, including the RAS-RAF-MEK-MAPK and the PI3K-Akt pathways [3]. Furthermore, the EGF receptor may stimulate angiogenesis in tumours by up-regulation of VEGF [39]. Thus, EGF receptor TKIs can target both tumour growth and angiogenesis. As discussed above, interference with angiogenesis may limit the clinical use of TKIs in SSc.

The role of the EGF receptor and its ligand tumour growth factor-α is well established in interstitial lung disease [40–44], and interaction of EGF and TGF-β signalling may impel the development of kidney fibrosis [45]. In SSc, however, only little evidence supports the clinical use of EGF receptor TKIs, such as erlotinib, gefitinib, lapatinib, and canertinib. *In vitro* experiments showed that EGF enhanced the expression of TGF-β receptors 2 in dermal fibroblasts suggesting pro-fibrotic effects of EGF signalling via the TGF-β pathway (fig. 1). Since EGF did not further up-regulate TGF-β receptors 2 on scleroderma fibroblasts, the true role of EGF signalling in SSc remains unknown [46]. Therefore, future studies may examine the effects of EGF signalling on fibrosis and evaluate anti-fibrotic effects of EGF receptor TKIs in SSc. Finally, anti-angiogenic (side) effects of EGF receptor TKIs require careful evaluation prior to clinical use in patients with SSc.

Conclusion

Progressive tissue fibrosis causes high morbidity and mortality in patients with SSc, but clearly effective anti-fibrotic therapies are not yet available for routine clinical use. Regarding its potent anti-fibrotic effects *in vitro* and *in vivo*, favourable pharmacokinetics, good clinical experiences regarding safety and toxicity in other diseases, and first promising case reports, the TKI imatinib is currently investigated in clinical proof-of-concept trials for the treatment of patients with SSc. We are awaiting critical data about safety and efficacy from these trials. Positive results will prompt larger placebo-controlled trials to establish imatinib for routine clinical use in SSc. The ongoing proof-of-concept trials will also provide important insights on general effects of the cytokine modulation in SSc. Besides ongoing investigations in SSc, observational studies showed promising results in the treatment of refractory sclerotic cGVHD with imatinib and might soon be succeeded by placebo-controlled trials.

In the meantime, further TKIs with potent, anti-fibrotic effects are emerging from preclinical studies. The dual c-Abl and PDGF receptor inhibitors nilotinib and dasatinib may be interesting alternatives to imatinib in the treatment of SSc. Because of their high receptor affinity, these agents might be more potent and lack some of the side effects of imatinib. Nilotinib and other TKIs of c-Abl and PDGF receptor might have positive effects on the proliferative vasculopathy of SSc in addition to their anti-fibrotic potential. Moreover, dasatinib paved the way for a group of new targets in anti-fibrotic therapy: selective inhibition of the non-receptor TKs Src may be another promising approach to prevent or even reduce tissue fibrosis in SSc.

In contrast to TKIs of c-Abl and PDGF receptor, the role of VEGF and EGF receptor TKIs in the treatment of SSc remains unclear. There is accumulating evidence that uncontrolled activation of VEGF receptor signalling contributes to tissue fibrosis in SSc and might mediate important features of the vasculopathy in SSc. However, there are important potential risks associated with inhibition of VEGF signalling including inhibition of wound healing. This needs to be carefully examined in preclinical models prior to the clinical use of VEGF receptor TKIs in SSc. The preclinical evidence for the anti-fibrotic efficacy of targeting EGF signalling is limited.

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References

1 Beyer C, Abraham D, Distler JH, Distler O. The pathogenesis of systemic sclerosis. In: Scleroderma – modern aspects of pathogenesis, diagnosis and therapy. Edited by Distler O. Bremen: UNI-MED Verlag AG; 2009: 23–32.

2 Arora A, Scholar EM. Role of tyrosine kinase inhibitors in cancer therapy. J Pharmacol Exp Ther. 2005;315(3):971–9.

3 Ciardiello F, Tortora G: EGFR antagonists in cancer treatment. N Engl J Med. 2008;358(11):1160–74.

4 Distler JH, Distler O. Intracellular tyrosine kinases as novel targets for anti-fibrotic therapy in systemic sclerosis. Rheumatology. (Oxford) 2008;47(Suppl 5):v10–11.

5 Hassoun PM, Mouthon L, Barbera JA, Eddahibi S, Flores SC, Grimminger F. et al. Inflammation, growth factors, and pulmonary vascular remodeling. J Am Coll Cardiol. 2009;54(1 Suppl):S10–19.

6 Daniels CE, Wilkes MC, Edens M, Kottom TJ, Murphy SJ, Limper AH, et al. Imatinib mesylate inhibits the profibrogenic activity of TGF-beta and prevents bleomycin-mediated lung fibrosis. J Clin Invest. 2004;114(9):1308–16.

7 Chen Y, Leask A, Abraham DJ, Pala D, Shiwen X, Khan K, et al. Heparan sulfate-dependent ERK activation contributes to the overexpression of fibrotic proteins and enhanced contraction by scleroderma fibroblasts. Arthritis Rheum. 2008;58(2):577–85.

8 Akhmetshina A, Dees C, Pileckyte M, Maurer B, Axmann R, Jungel A. et al. Dual inhibition of c-abl and PDGF receptor signaling by dasatinib and nilotinib for the treatment of dermal fibrosis. Faseb J. 2008;22(7):2214–22.

9 Distler JH, Jungel A, Huber LC, Schulze-Horsel U, Zwerina J, Gay RE, et al. Imatinib mesylate reduces production of extracellular matrix and prevents development of experimental dermal fibrosis. Arthritis Rheum. 2007;56(1):311–22.

10 Akhmetshina A, Venalis P, Dees C, Busch N, Zwerina J, Schett G, et al. Treatment with imatinib prevents fibrosis in different preclinical models of systemic sclerosis and induces regression of established fibrosis. Arthritis Rheum. 2009;60(1):219–24.

11 Abdollahi A, Li M, Ping G, Plathow C, Domhan S, Kiessling F, et al. Inhibition of platelet-derived growth factor signaling attenuates pulmonary fibrosis. J Exp Med. 2005;201(6):925–35.

12 Wang S, Wilkes MC, Leof EB, Hirschberg R. Imatinib mesylate blocks a non-Smad TGF-beta pathway and reduces renal fibrogenesis in vivo. Faseb J. 2005;19(1):1–11.

13 Yoshiji H, Noguchi R, Kuriyama S, Ikenaka Y, Yoshii J, Yanase K, et al. Imatinib mesylate (STI-571) attenuates liver fibrosis development in rats. Am J Physiol Gastrointest Liver Physiol. 2005;288(5):G907–13.

14 Rajkumar VS, Shiwen X, Bostrom M, Leoni P, Muddle J, Ivarsson M, et al. Platelet-derived growth factor-beta receptor activation is essential for fibroblast and pericyte recruitment during cutaneous wound healing. Am J Pathol. 2006;169(6):2254–65.

15 Atallah E, Kantarjian H, Cortes J. Emerging safety issues with imatinib and other Abl tyrosine kinase inhibitors. Clin Lymphoma Myeloma. 2007;7(Suppl 3):S105–12.

16 Druker BJ, Guilhot F, O'Brien SG, Gathmann I, Kantarjian H, Gattermann N, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. N Engl J Med. 2006;355(23):2408–17.

17 Distler JH, Distler O. Cardiotoxicity of imatinib mesylate: an extremely rare phenomenon or a major side effect? Ann Rheum Dis. 2007;66(6):836.

18 Kerkela R, Grazette L, Yacobi R, Iliescu C, Patten R, Beahm C, et al. Cardiotoxicity of the cancer therapeutic agent imatinib mesylate. Nat Med. 2006;12(8):908–16.

19 Beham-Schmid C, Apfelbeck U, Sill H, Tsybrovsky O, Hofler G, Haas OA, et al. Treatment of chronic myelogenous leukemia with the tyrosine kinase inhibitor STI571 results in marked regression of bone marrow fibrosis. Blood. 2002;99(1):381–3.

20 Bueso-Ramos CE, Cortes J, Talpaz M, O'Brien S, Giles F, Rios MB, et al. Imatinib mesylate therapy reduces bone marrow fibrosis in patients with chronic myelogenous leukemia. Cancer. 2004;101(2):332–6.

21 Kay J, High WA. Imatinib mesylate treatment of nephrogenic systemic fibrosis. Arthritis Rheum. 2008;58(8):2543–8.

22 Sabnani I, Zucker MJ, Rosenstein ED, Baran DA, Arroyo LH, Tsang P, et al. A novel therapeutic approach to the treatment of scleroderma-associated pulmonary complications: safety and efficacy of combination therapy with imatinib and cyclophosphamide. Rheumatology. (Oxford) 2009;48(1):49–52.

23 Sfikakis PP, Gorgoulis VG, Katsiari CG, Evangelou K, Kostopoulos C, Black CM: Imatinib for the treatment of refractory, diffuse systemic sclerosis. Rheumatology. (Oxford) 2008;47(5):735–7.

24 van Daele PL, Dik WA, Thio HB, van Hal PT, van Laar JA, Hooijkaas H, et al. Is imatinib mesylate a promising drug in systemic sclerosis? Arthritis Rheum. 2008;58(8):2549–52.

25 Magro L, Mohty M, Catteau B, Coiteux V, Chevallier P, Terriou L, et al. Imatinib mesylate as salvage therapy for refractory sclerotic chronic graft-versus-host disease. Blood. 2009;114(3):719–22.

26 Olivieri A, Locatelli F, Zecca M, Sanna A, Cimminiello M, Raimondi R, et al. Imatinib for refractory chronic graft-versus-host disease with fibrotic features. Blood. 2009;114(3):709–18.

27 Distler JH, Manger B, Spriewald BM, Schett G, Distler O. Treatment of pulmonary fibrosis for twenty weeks with imatinib mesylate in a patient with mixed connective tissue disease. Arthritis Rheum. 2008;58(8):2538–42.

28 Quintas-Cardama A, Kantarjian H, Cortes J. Imatinib and beyond – exploring the full potential of targeted therapy for CML. Nat Rev Clin Oncol. 2009;6(9):535–43.

29 Maurer B, Busch N, Jüngel A, Gay RE, Schett G, Michel BA, et al. Tyrosine Kinase Inhibitors (TKI) Are Promising Therapeutic Agents for the Proliferative Vasculopathy in SSc [abstract]. Arthritis Rheum. 2009;60(Suppl 10):1263.

30 Skhirtladze C, Distler O, Dees C, Akhmetshina A, Busch N, Venalis P et al: Src kinases in systemic sclerosis: central roles in fibroblast activation and in skin fibrosis. Arthritis Rheum. 2008;58(5):1475–84.

31 Okutani D, Lodyga M, Han B, Liu M. Src protein tyrosine kinase family and acute inflammatory responses. Am J Physiol Lung Cell Mol Physiol. 2006;291(2):L129–41.

32 Distler O, Distler JH, Scheid A, Acker T, Hirth A, Rethage J, et al. Uncontrolled expression of vascular endothelial growth factor and its receptors leads to insufficient skin angiogenesis in patients with systemic sclerosis. Circ Res. 2004;95(1):109–16.

33 Dor Y, Djonov V, Abramovitch R, Itin A, Fishman GI, Carmeliet P, et al. Conditional switching of VEGF provides new insights into adult neovascularization and pro-angiogenic therapy. Embo J. 2002;21(8):1939–47.

34 Drake CJ, Little CD. Exogenous vascular endothelial growth factor induces malformed and hyperfused vessels during embryonic neovascularization. Proc Natl Acad Sci. USA 1995;92(17):7657–61.

35 Sundberg C, Nagy JA, Brown LF, Feng D, Eckelhoefer IA, Manseau EJ, et al. Glomeruloid microvascular proliferation follows adenoviral vascular permeability factor/vascular endothelial growth factor-164 gene delivery. Am J Pathol. 2001;158(3):1145–60.

36 Beyer C, Schett G, Gay S, Distler O, Distler JH. Hypoxia. Hypoxia in the pathogenesis of systemic sclerosis. Arthritis Res Ther. 2009;11(2):220.

37 Distler JH, Jungel A, Pileckyte M, Zwerina J, Michel BA, Gay RE, et al. Hypoxia-induced increase in the production of extracellular matrix proteins in systemic sclerosis. Arthritis Rheum. 2007;56(12):4203–15.

38 Maurer B, Akhmetshina A, Gay RE, Schett G, Michel BA, Detmar M, et al. VEGF Aggravates Skin Fibrosis in Different Animal Models of Systemic Sclerosis (SSc) [abstract]. Arthritis Rheum. 2009;60(Suppl 10):1060.

39 Petit AM, Rak J, Hung MC, Rockwell P, Goldstein N, Fendly B, et al. Neutralizing antibodies against epidermal growth factor and ErbB-2/neu receptor tyrosine kinases down-regulate vascular endothelial growth factor production by tumor cells in vitro and in vivo: angiogenic implications for signal transduction therapy of solid tumors. Am J Pathol. 1997;151(6):1523–30.

40 Liu JY, Morris GF, Lei WH, Corti M, Brody AR. Up-regulated expression of transforming growth factor-alpha in the bronchiolar-alveolar duct regions of asbestos-exposed rats. Am J Pathol. 1996;149(1):205–17.

41 Madtes DK, Busby HK, Strandjord TP, Clark JG. Expression of transforming growth factor-alpha and epidermal growth factor receptor is increased following bleomycin-induced lung injury in rats. Am J Respir Cell Mol Biol. 1994;11(5):540–51.

42 Van Winkle LS, Isaac JM, Plopper CG. Distribution of epidermal growth factor receptor and ligands during bronchiolar epithelial repair from naphthalene-induced Clara cell injury in the mouse. Am J Pathol. 1997;151(2):443–59.

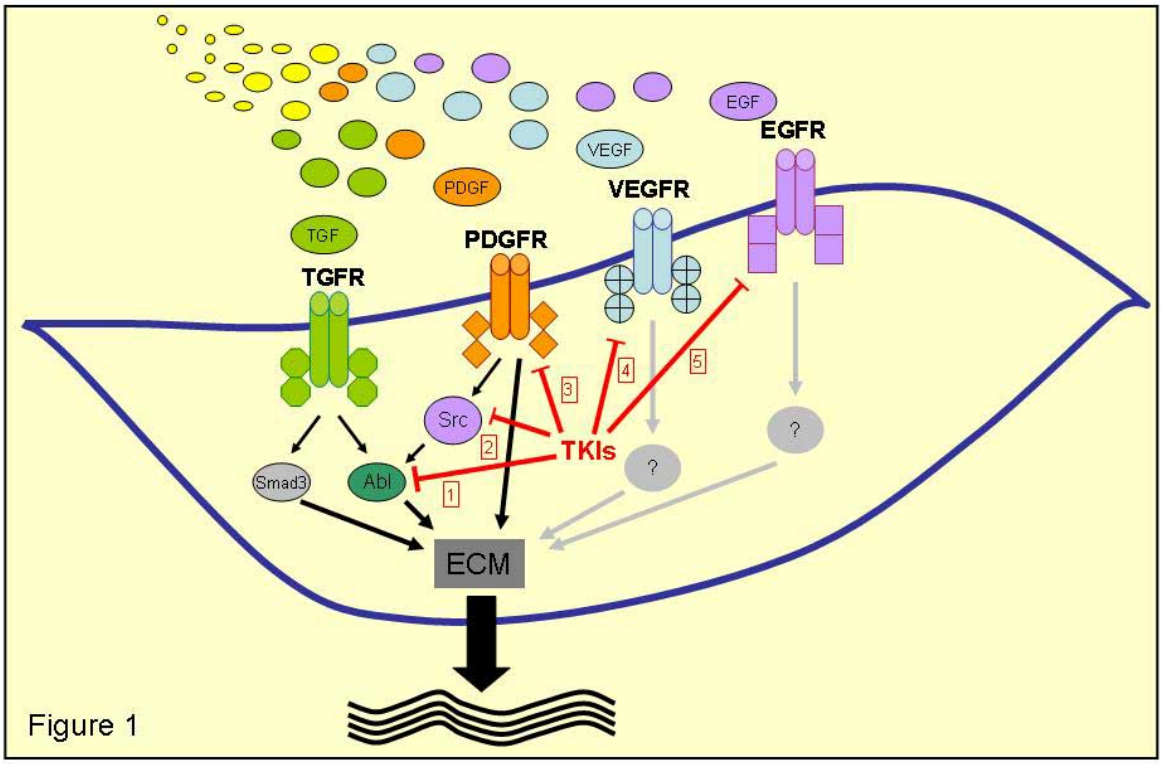
43 Waheed S, D'Angio CT, Wagner CL, Madtes DK, Finkelstein JN, Paxhia A, et al. Transforming growth factor alpha (TGF(alpha)) is increased during hyperoxia and fibrosis. Exp Lung Res. 2002;28(5):361–72.

44 Hardie WD, Davidson C, Ikegami M, Leikauf GD, Le Cras TD, Prestridge A, et al. EGF receptor tyrosine kinase inhibitors diminish transforming growth factor-alpha-induced pulmonary fibrosis. Am J Physiol Lung Cell Mol Physiol. 2008;294(6):L1217–25.

45 Cho HJ, Kang JH, Kim T, Park KK, Kim CH, Lee IS, et al. Suppression of PAI-1 expression through inhibition of the EGFR-mediated signaling cascade in rat kidney fibroblast by ascofuranone. J Cell Biochem. 2009;107(2):335–44.

46 Yamane K, Ihn H, Tamaki K. Epidermal growth factor up-regulates expression of transforming growth factor beta receptor type II in human dermal fibroblasts by phosphoinositide 3-kinase/Akt signaling pathway: Resistance to epidermal growth factor stimulation in scleroderma fibroblasts. Arthritis Rheum. 2003;48(6):1652–66.

Figure 1
Targeting tyrosine kinases in Systemic Sclerosis.



Transmembrane (TGF-β, PDGF, VEGF, and EGF receptors) as well as intracellular (c-Abl and Src kinases) tyrosine kinases promote the production and release of extracellular matrix (ECM) proteins. Pro-fibrotic downstream signaling of TGF-β and PGDF is well-established and involves Smad proteins, c-Abl, and Src kinases. By contrast, downstream pathways of VEGF and EGF that promote ECM synthesis in SSc fibroblasts still need in detail- characterisation. Regarding their central role in production and release of ECM, tyrosine kinases are promising targets for anti-fibrotic treatment approaches in SSc since they can be blocked by specific inhibitors (TKIs). 1) Imatinib, dasatinib, and nilotinib block the intracellular tyrosine kinase c-Abl, a downstream target of pro-fibrotic TGF-β signaling. 2) In addition to its effects on c-Abl and the PDGF receptor, dasatinib inhibits Src kinases, which link increased PDGF receptor activity with activation of c-Abl. 3) Imatinib, dasatinib, and nilotinib are inhibitors of the PDGF receptor, which can promote ECM production directly or via activation of Src kinases and c-Abl. 4) Semaxinib, vatalanib, sutent, and sorafenib block VEGF receptor signalling and might decrease ECM production. The exact mechanisms liniking VEGF receptor signalling and ECM synthesis are still unclear. 5) Erlotinib, gefitinib, lapatinib, and canertinib block EGF receptors. Although downstream pathways of EGF signalling are only partially explored in SSc, activation of EGF receptors might contribute to increased synthesis of ECM in SSc fibroblasts.