The scientific basis for novel treatments of systemic sclerosis

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Abstract

In recent years, many potential antifibrotic treatment strategies have emerged from molecular studies of systemic sclerosis. Few biologicals have already entered clinical trials and these may hopefully prove to be effective in this progressive, profibrotic disease.

Introduction and context

Vasculopathy, autoimmunity, and fibrosis are hallmarks of systemic sclerosis (SSc), a profibrotic disease that affects the skin and multiple internal organs, including the lungs, kidneys, gut, and heart [1]. In the late stages of SSc, progressive tissue fibrosis and organ failure cause high morbidity and increased mortality. Therapeutic options to treat patients with SSc symptomatically are limited, and causal therapies do not exist. In recent years, however, researchers have identified several key profibrotic molecules in the pathogenesis of SSc and have developed antifibrotic therapies, which now can be evaluated in clinical studies. Findings in preclinical models of SSc raised hopes that these antifibrotic therapeutics might restrain tissue fibrosis and alleviate patients' symptoms. Because of their mode of action, however, the antifibrotic therapies cannot target vasculopathy and autoimmune disease in patients with SSc. To develop causal treatment strategies, we still need to learn more about the pathogenesis of SSc.

Recent advances

Both *in vitro* and *in vivo* studies indicate the central role of transforming growth factor-beta (TGF- β) in the development of fibrosis in SSc. TGF- β stimulates fibroblasts to produce excessive amounts of extracellular matrix proteins, the predominant components of fibrotic tissue. Thus, inhibition of TGF- β signaling can reduce tissue fibrosis in experimental models of SSc [2]. Nevertheless, recombinant TGF- β_1 -neutralizing antibodies (CAT-192)

failed to show efficacy in the first multi-center randomized placebo-controlled phase I/II trial [3]. Insufficient affinity to TGF- β_1 *in vivo* might explain treatment failure with the CAT-192 antibodies (Figure 1).

Imatinib interferes with two important profibrotic pathways in SSc as it inhibits the TGF- β downstream kinase c-Abl and the tyrosine kinase activity of platelet-derived growth factor (PDGF) receptors [4]. In a murine model of radiation-induced pulmonary injury, imatinib inhibited the development of lung fibrosis [5]. In several experimental models of SSc, we demonstrated that imatinib prevented the development of fibrosis and reduced established skin fibrosis, suggesting its efficacy in both early and late stages of the disease [6,7]. Of note, smaller clinical studies in patients with chronic myelogenous leukemia (CML), in which imatinib is a first-line therapy, demonstrated regression of bone marrow fibrosis [8,9]. In addition, the first case reports indicated that imatinib mesylate could reduce established fibrosis in patients with SSc, mixed connective tissue disease, and nephrogenic fibrosis [10-12]. As shown by two recent studies, imatinib is highly effective in patients with refractory chronic graft-versus-host disease, which shares several pathologic features with SSc, including progressive skin fibrosis [13,14]. The antifibrotic effects in experimental models of SSc, its efficacy in other profibrotic disorders, and the large clinical experience from the treatment of CML prompted clinical trials currently evaluating the efficacy of imatinib in patients with SSc.

Figure 1. Novel antifibrotic therapies in systemic sclerosis (SSc)

Excessive accumulation of extracellular matrix (ECM) causes severe tissue fibrosis in SSc. Antifibrotic therapies target profibrotic pathways in fibroblasts, the main producers of ECM. ¹CAT-192 anti-transforming growth factor- β antibodies (TGF- β ab) catch TGF- β molecules (TGF), which would bind to TGF- β receptors (TGF β R) to activate potent profibrotic pathways. Smad molecules, including Smad 3, as well as the Abelson kinase (Abi) are downstream mediators of the profibrotic TGF- β pathway. ²Receptor tyrosine kinase inhibitors (RTKI) can block several profibrotic signaling cascades. Imatinib and nilotinib inhibit both Abi and the platelet-derived growth factor receptor (PDGFR). In addition to Abi and PDGFR, dasatinib blocks Src kinases (Src). ³The thiazolidinediones, a group of peroxisome proliferator-activated receptor- γ agonists (PPAR- γ A), bind to their intra-nuclear receptors to inhibit ECM production. ⁴Histone deacetylase inhibitors (HDACi) as well as ⁵DNA methyltransferase inhibitors (DNMTi) decrease ECM production by modifying gene transcription.

Dasatinib and nilotinib, two novel inhibitors of c-Abl and the PDGF receptor, serve as salvage therapies for the treatment of refractory CML and in patients with intolerance to imatinib [15]. Similar to imatinib, dasatinib and nilotinib inhibited the development of fibrosis in *in vitro* and *in vivo* models of SSc and therefore might be interesting alternatives in the antifibrotic treatment with tyrosine kinase inhibitors. In addition to its direct effects on c-Abl and the PDGF receptor, dasatinib inhibits Src kinases. These enzymes regulate the activation of c-Abl and are activated by profibrotic cytokines, such as TGF- β and PDGF. In experimental models of SSc, the specific inhibitor of Src kinase, SU6656, reduced the development of dermal fibrosis. Thus, targeting of Src kinases may be another promising approach in the treatment of SSc [16].

Peroxisome proliferator-activated receptor- γ (PPAR- γ) is a member of the nuclear hormone receptor superfamily, which can activate a number of biological effects, including alterations in metabolic and inflammatory responses. The thiazolidinediones, a group of clinically approved PPAR- γ agonists, lower blood glucose levels in patients with type 2 diabetes. PPAR- γ agonists also suppressed cell activation and collagen

production in skin and lung fibroblasts and inhibited the development of fibrosis in murine models [17-19].

As targeted therapies in patients with malignancies, histone deacetylase (HDAC) inhibitors induce cell cycle arrest, cell differentiation, and apoptotic cell death of tumor cells [20]. Besides the cytotoxic effects on tumor cells, HDAC inhibitors can reduce the development of TGF- β - and PDGF-induced fibrosis in experimental models of SSc. The non-selective inhibitor trichostatin A (TSA) inhibited TGF- β signaling by preventing the nuclear translocation and the DNA binding of Smad3/Smad4 complexes in dermal fibroblasts. Upregulation of the cell cycle inhibitor p21 upon treatment with TSA may also reduce activation of fibroblasts and excessive production of extracellular matrix components [21]. Since the first clinical trials in patients with malignancies reported low toxicity, the antifibrotic effects in the preclinical models encourage clinical trials with TSA in SSc patients. Selective HDAC inhibitors (e.g., against HDAC-7) might offer even higher efficacy and lower toxicity [22].

Similar to HDACs, DNA methyltransferases (DNMTs) regulate DNA transcription by modifying the accessibility of genes to the transcription machinery. *In vitro* experiments demonstrated that the DNMT inhibitor 5-Aza-2-deoxycytidine decreased the release of collagen by restoring the transcription of *Fli-1*, which is hyper-methylated and thereby silenced in SSc fibroblasts [23]. Furthermore, we showed that 5-Aza-2-deoxycytidine and other inhibitors of DNMTs, including procainamide and hydralazine, prevented the development of fibrosis in *in vivo* models of SSc [24].

Implications for clinical practice

The thorough work of many researchers in our field has led to a better understanding of profibrotic pathways, the identification of target molecules, and the development of new therapeutic strategies in SSc. The tyrosine kinase inhibitor imatinib is currently under clinical evaluation for the treatment of patients with SSc and we are awaiting critical data from these trials. In contrast, the failure of the TGF- β ₁-neutralizing CAT-192 antibodies *in vivo* requires further investigation. Since the pathogenesis of SSc remains enigmatic, we still face a lot of work to develop causal therapies for the treatment of SSc.

Abbreviations

CML, chronic myelogenous leukemia; DNMT, DNA methyltransferase; HDAC, histone deacetylase; PDGF, platelet-derived growth factor; PPAR- γ , peroxisome proliferator-activated receptor- γ ; SSc, systemic sclerosis; TGF- β , transforming growth factor-beta; TSA, trichostatin A.

Competing interests

JHWD is involved in a clinical trial of imatinib in SSc that is sponsored by Novartis International AG (Basel, Switzerland). In addition, JHWD received grants from the Deutsche Forschungsgesellschaft (German Research Foundation), Interdisciplinary Center for Clinical Research in Erlangen, the Wilhelm Sander Foundation, and the Ernst Jung Foundation Career Support Award. JHWD has scientific cooperation with Novartis Pharmaceuticals, Array BioPharma (Boulder, CO, USA), Bayer Schering Pharma AG (Berlin-Wedding, Germany), Bristol-Myers Squibb (New York, NY, USA), Celgene Corporation (Summit, NJ, USA), and ErgoNex Pharma GmbH (Appenzell, Switzerland). JHWD received speaker fees from Actelion Pharmaceuticals Ltd (Allschwil, Switzerland), Encysive Pharmaceuticals (now part of Pfizer, Inc., New York, NY, USA), and GlaxoSmith-Kline (Brentford, Middlesex, UK). CB declares that he has no competing interests.

References

- 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, Germany: UNI-MED Verlag AG; 2009:23-42.
- Varga J, Pasche B: **Transforming growth factor beta as a therapeutic target in systemic sclerosis.** *Nat Rev Rheumatol* 2009, **5**:200-6.
- Denton CP, Merkel PA, Furst DE, Khanna D, Emery P, Hsu VM, Silliman N, Streisand J, Powell J, Akesson A, Coppock J, Hoogen F, Herrick A, Mayes MD, Veale D, Haas J, Ledbetter S, Korn JH, Black CM, Seibold JR; Cat-192 Study Group; Scleroderma Clinical Trials Consortium: **Recombinant human anti-transforming growth factor beta1 antibody therapy in systemic sclerosis: a multicenter, randomized, placebo-controlled phase I/II trial of CAT-192.** *Arthritis Rheum* 2007, **56**:323-33.
- Distler JH, Distler O: **Imatinib as a novel therapeutic approach for fibrotic disorders.** *Rheumatology (Oxford)* 2009, **48**:2-4.
- Abdollahi A, Li M, Ping G, Plathow C, Domhan S, Kiessling F, Lee LB, McMahon G, Gröne HJ, Lipson KE, Huber PE: **Inhibition of platelet-derived growth factor signaling attenuates pulmonary fibrosis.** *J Exp Med* 2005, **201**:925-35.
- Akhmetshina A, Venalis P, Dees C, Busch N, Zwerina J, Schett G, Distler O, Distler JH: **Treatment with imatinib prevents fibrosis in different preclinical models of systemic sclerosis and induces regression of established fibrosis.** *Arthritis Rheum* 2009, **60**:219-24.
- Distler JH, Jüngel A, Huber LC, Schulze-Horsel U, Zwerina J, Gay RE, Michel BA, Hauser T, Schett G, Gay S, Distler O: **Imatinib mesylate reduces production of extracellular matrix and prevents development of experimental dermal fibrosis.** *Arthritis Rheum* 2007, **56**:311-22.
- Beham-Schmid C, Apfelbeck U, Sill H, Tsybrovsky O, Hofler G, Haas OA, Linkesch W: **Treatment of chronic myelogenous leukemia with the tyrosine kinase inhibitor STI571 results in marked regression of bone marrow fibrosis.** *Blood* 2002, **99**:381-3.
- Bueso-Ramos CE, Cortes J, Talpaz M, O'Brien S, Giles F, Rios MB, Medeiros LJ, Kantarjian H: **Imatinib mesylate therapy reduces bone marrow fibrosis in patients with chronic myelogenous leukemia.** *Cancer* 2004, **101**:332-6.
- 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**:2538-42.

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- Kay J, High WA: **Imatinib mesylate treatment of nephrogenic systemic fibrosis.** *Arthritis Rheum* 2008, **58**:2543-8.
- 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**:735-7.
- Magro L, Mohty M, Catteau B, Coiteux V, Chevallier P, Terriou L, Jouet JP, Yakoub-Agha I: **Imatinib mesylate as salvage therapy for refractory sclerotic chronic graft-versus-host disease.** *Blood* 2009, **114**:719-22.
- Olivieri A, Locatelli F, Zecca M, Sanna A, Cimminiello M, Raimondi R, Gini G, Mordini N, Balduzzi A, Leoni P, Gabrielli A, Bacigalupo A: **Imatinib for refractory chronic graft-versus-host disease with fibrotic features.** *Blood* 2009, **114**:709-18.
- 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**:535-43.
- Skhirdadze C, Distler O, Dees C, Akhmetshina A, Busch N, Venalis P, Zwerina J, Spriewald B, Pileckyte M, Schett G, Distler JH: **Src kinases in systemic sclerosis: central roles in fibroblast activation and in skin fibrosis.** *Arthritis Rheum* 2008, **58**:1475-84.
- Aoki Y, Maeno T, Aoyagi K, Ueno M, Aoki F, Aoki N, Nakagawa J, Sando Y, Shimizu Y, Suga T, Arai M, Kurabayashi M: **Pioglitazone, a peroxisome proliferator-activated receptor gamma ligand, suppresses bleomycin-induced acute lung injury and fibrosis.** *Respiration* 2009, **77**:311-9.
- Burgess HA, Daugherty LE, Thatcher TH, Lakatos HF, Ray DM, Redonnet M, Phipps RP, Sime PJ: **PPARgamma agonists inhibit TGF-beta induced pulmonary myofibroblast differentiation and collagen production: implications for therapy of lung fibrosis.** *Am J Physiol Lung Cell Mol Physiol* 2005, **288**:L1146-53.
- Milam JE, Keshamouni VG, Phan SH, Hu B, Gangireddy SR, Hogaboam CM, Standiford TJ, Thannickal VJ, Reddy RC: **PPAR-gamma agonists inhibit profibrotic phenotypes in human lung fibroblasts and bleomycin-induced pulmonary fibrosis.** *Am J Physiol Lung Cell Mol Physiol* 2008, **294**:L891-901.
- Monneret C: **Histone deacetylase inhibitors.** *Eur J Med Chem* 2005, **40**:1-13.
- Huber LC, Distler JH, Moritz F, Hemmatazad H, Hauser T, Michel BA, Gay RE, Matucci-Cerinic M, Gay S, Distler O, Jüngel A: **Trichostatin A prevents the accumulation of extracellular matrix in a mouse model of bleomycin-induced skin fibrosis.** *Arthritis Rheum* 2007, **56**:2755-64.
- Hemmatazad H, Rodrigues HM, Maurer B, Brentano F, Pileckyte M, Distler JH, Gay RE, Michel BA, Gay S, Huber LC, Distler O, Jüngel A: **Histone deacetylase 7, a potential target for the antifibrotic treatment of systemic sclerosis.** *Arthritis Rheum* 2009, **60**:1519-29.
- Wang Y, Fan PS, Kahaleh B: **Association between enhanced type I collagen expression and epigenetic repression of the FLII gene in scleroderma fibroblasts.** *Arthritis Rheum* 2006, **54**:2271-9.
- Dees C, Akhmetshina A, Busch N, Horn A, Gusinde J, Nevskaya T, Jüngel A, Gay S, Distler O, Schett G, Distler JH: **Inhibitors of DNA methyltransferases exert potent anti-fibrotic effects via reactivation of SOCS-3.** Paper presented at EULAR 2009, the Annual European Congress of Rheumatology of the European League Against Rheumatism; 10-13 June 2009; Copenhagen, Denmark.

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