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Review

Tyrosine kinase signaling in fibrotic disorders Translation of basic research to human disease

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ABSTRACT

Tyrosine kinases regulate a broad variety of physiological cell processes, including metabolism, growth, differentiation and apoptosis. Abnormal tyrosine kinase activity disturbs the physiological cell homeostasis and can lead to cancer, vascular disease, and fibrosis. In regard to fibrosis, different tyrosine kinases have been identified as determinants of disease progression and potential targets for anti-fibrotic therapies. This includes both receptor tyrosine kinases (e.g., PDGF receptor, VEGF receptor, EGF receptor, and JAK kinases) as well as non-receptor tyrosine kinases (e.g., c-Abl, c-Kit, and Src kinases). Given their central role in the pathogenesis of fibrosis, researchers of our field study the anti-fibrotic effects of monoclonal antibodies or small-molecule inhibitors to block the aberrant tyrosine kinase activity and treat fibrosis in preclinical models of various fibrotic diseases (e.g., idiopathic pulmonary fibrosis, renal fibrosis, liver fibrosis, and dermal fibrosis). The results of these studies were promising and prompted clinical trials with different compounds in fibrotic diseases. So far, results from studies with intedanib in idiopathic pulmonary fibrosis and imatinib in idiopathic pulmonary fibrosis and systemic sclerosis have been reported. Although none of these studies reported a positive primary outcome, promising trends in anti-fibrotic efficacy awaken our hopes for a new class of effective anti-fibrotic targeted therapies. This article is part of a Special Issue entitled: Fibrosis: Translation of basic research to human disease.

1. Introduction

Tyrosine kinases regulate a wide variety of physiological cell processes, including metabolism, growth, differentiation, and apoptosis. The common mode of action of tyrosine kinases is phosphorylation of target proteins at tyrosine residues, which allows formation of multiprotein complexes critical in signal transduction. Depending on their localization in the cell, tyrosine kinases can be classified in two major groups: the receptor tyrosine kinases are membrane receptors that activate intracellular signaling pathways upon ligand binding to their extracellular domains. For most of the receptor tyrosine kinases, this process includes the di- or oligomerization of tyrosine kinase monomers, followed by autophosphorylation of the intracellular kinase domain to increase the catalytic activity. After autophosphorylation, the receptor tyrosine kinases recruit and phosphorylate cytoplasmic signaling molecules either directly or indirectly via docking proteins that are also phosphorylated by receptor tyrosine kinases [1]. In contrast to receptor tyrosine kinases, non-receptor tyrosine kinases lack extracellular and transmembrane domains but modulate signaling pathways within the cytoplasm. Similar to receptor tyrosine kinases, phosphorylation and autophosphorylation lead to activation of non-receptor tyrosine kinases [2].

Given the central role of receptor and non-receptor tyrosine kinases in cell signaling, deregulated tyrosine kinase activity can promote the development and progression of neoplastic, cardiovascular, and fibrotic diseases. In this context, pathologic activation of tyrosine kinases can drive cancerogenesis, vascular remodeling, and fibrogenesis [3–5], suggesting that restoral of normal tyrosine kinase activity may be an effective treatment approach in each of these conditions. So far, two different pharmacological strategies can target the pathologic tyrosine kinase activity: monoclonal antibodies block the extracellular domains of receptor tyrosine kinases, while small molecule inhibitors enter the cell and block kinase domains of both receptor and non-receptor tyrosine kinases. Of note, several compounds of both classes are already considered first-line therapies in various malignancies. This includes antibodies against epithelial growth factor (EGF) receptor (e.g., trastuzumab) in HER2-positive breast cancer patients or the small molecule inhibitor imatinib, which blocks the aberrant activity of the Abelson kinase in chronic myelogenous leukemia (CML). Interestingly, treatment of CML with imatinib provided the first clinical evidence for potential anti-fibrotic effects of tyrosine kinase inhibition: imatinib led to regression of bone marrow fibrosis in CML patients, an effect independent of the anti-tumor activity [6,7]. Stimulated by these findings, research in our field intensified basic and translational studies on the role of tyrosine kinases in the development

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of fibrosis as well as the potential translational implications for the treatment of fibrotic diseases.

Pathologic activation of fibroblasts and related cells is a hallmark of fibrotic diseases, including idiopathic pulmonary fibrosis (IPF), renal fibrosis, liver fibrosis or systemic sclerosis (SSc). During early stages of fibrotic disease, tissue damage and inflammation are thought to activate fibroblasts, while para- and autostimulatory loops may dominate later disease stages. Once activated, fibroblasts can express contractile proteins (e.g., α-smooth muscle actin) and release excessive amounts of extracellular matrix components. The fibrotic process culminates in pathologic tissue scarring and failure of the affected organs.

As we will discuss in this review, various tyrosine kinases play key roles in the pathologic activation of fibroblasts during fibrogenesis (Fig. 1), rendering them attractive molecular targets in the treatment of fibrosis. Paying tribute to the large body of evidence, we will particularly focus on the role of tyrosine kinases in SSc but also highlight important findings in other fibrotic diseases. The first part of our review will describe the molecular pathways of pro-fibrotic tyrosine kinase activity as well as translational findings obtained with tyrosine kinase inhibitors in experimental models of fibrosis. In the second part, we will discuss recent findings of published clinical trials with tyrosine kinase inhibitors in SSc and other fibrotic diseases.

2. Tyrosine kinases as modulators of fibroblast activation

2.1. PDGF receptors

The platelet derived growth factor receptors (PDGFRs) α and β are receptor tyrosine kinases that bind members of the PDGF family of growth factors. Upon activation, PDGFR monomers hetero- or homodimerize to PDGFRαα, PDGFRαβ and PDGFRββ to induce autophosphorylation and activate downstream signaling cascades. PDGFRα and β show similar structures and activate overlapping signal transduction pathways, including phosphatidylinositol 3 kinase (PI3K), Ras-MAP kinases, Src family kinases and phospholipase Cγ (PLCγ), which results in partly overlapping biological activities. In addition to dimerization of distinct receptor monomers, PDGF ligands (i.e., PDGF-A, B, C and D) form different homo- or heterodimers that vary in their affinity for the different receptor complexes [8].

PDGF-A/PDGFRα and PDGF-B/PDGFRβ interactions have different biological roles. In general, PDGF-B/PDGFRβ-signaling appears to be prominent in vascular remodeling, both for normal homeostasis and pathologic conditions. For example, pericyte coverage of blood vessels is particularly dependent on PDGF-B/PDGFRβ-signaling [9]. PDGF-B is primarily released by macrophages and hepatic stellate cells, with the latter ones also pointing to a major role of PDGF-B/PDGFRβ-signaling in liver fibrosis [10,11]. By contrast, PDGF-A/PDGFRα signaling appears to have a broader role in tissue homeostasis and repair, in particular in the skin, lungs, gut and kidneys. Fibroblasts and fibroblast-like cells are both major sources and targets for PDGF-A since they express PDGFRα on their cell surface [12–14]. Thus, paracrine and autocrine PDGF-A/PDGFRα signaling loops can stimulate fibroblasts to synthesize extracellular matrix and release pro-fibrotic mediators. Discovered more recently, the roles of PDGF-C and D in tissue homoeostasis and fibrotic disease of various organs are less well-defined. While PDGF-C may primarily activate PDGFRα, PDGFRβ appears to be the main receptor for PDGF-D [15].

PDGF signaling remains silent in most normal tissues but becomes activated upon tissue injury to promote wound closure and scar formation. During wound healing, PDGF signaling is tightly regulated and turned off as soon as the repair processes are completed [16]. Uncontrolled activation or failure to terminate activated PDGF signaling may lead to excessive scar formation and tissue fibrosis. In this context, enhanced PDGF signaling has been described in pulmonary fibrosis and SSc (mainly PDGF-A via PDGFRα) as well as in liver fibrosis (PDGF-B via PDGFRβ). In addition, there is increasing evidence for pro-fibrotic effects of PDGF-C and D (via PDGFRα and PDGFRβ) in the liver and the kidneys [15,17–21]. Of note, an additional, PDGF-independent mechanism may activate PDGF signaling in SSc: stimulatory autoantibodies directed against the PDGF receptors were found to be capable of stimulating reactive oxygen species to activate pro-fibrotic ERK signaling [22].

The role of PDGF signaling in the development of tissue fibrosis is further corroborated by murine models harboring mutations for the PDGF receptor α or β. Animals with activating mutations for the PDGF receptor α develop progressive fibrosis of the skin, gastrointestinal tract, kidneys, heart, and skeletal muscles, but do not show perturbed vascular integrity and smooth muscle activity, which is consistent to the minor role of PDGF-A/PDGFRα signaling in blood vessels [14]. In contrast, experimental activation of PDGFRβ has a major impact on cell proliferation in aortic smooth muscle cells in vivo [9].

Given the central role of PDGF in tissue fibrosis, blockade of the PDGFR appears to be a promising anti-fibrotic treatment approach.

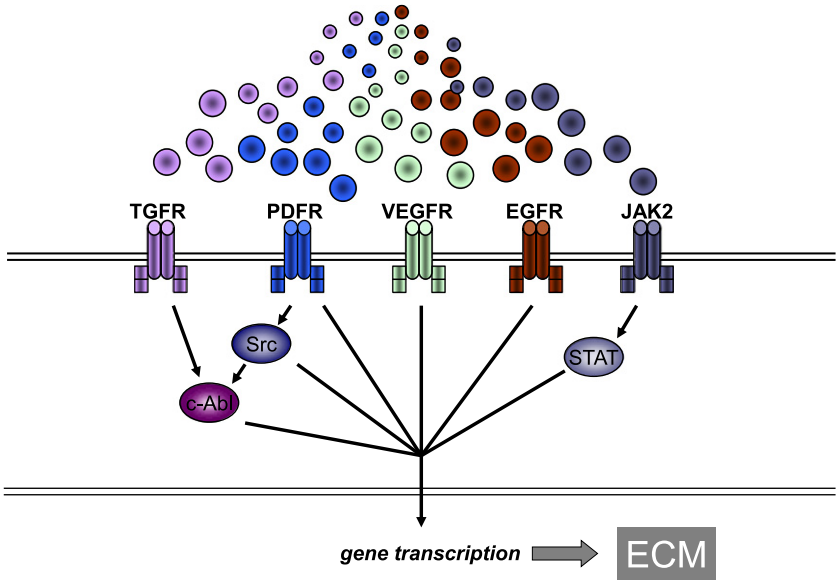

Fig. 1. Tyrosine kinases with central roles in fibrosis. Receptor tyrosine kinases, including PDGFR, VEGFR, EGFR and JAK kinases as well as non-receptor tyrosine kinases, such as c-Abl and Src kinases, stimulate the pathological synthesis and release of extracellular matrix (ECM) proteins.

Imatinib, a small molecule tyrosine kinase inhibitor, targets the kinase domain of the PDGFR. Apart from its effects on PDGF signaling, imatinib also interferes with the tyrosine kinases c-Abl and c-Kit, which are discussed later in this review [23]. In vitro and in vivo, blockade of the PDGFR by imatinib inhibited the activation of fibroblasts, the release of extracellular matrix and the development of experimental fibrosis in model systems for dermal, pulmonary, renal and liver fibrosis [24–29]. In some models, imatinib was effective in preventing the development of fibrosis as well as reducing established fibrosis [30].

Since most studies evaluating pharmacological PDGF blockade in fibrosis have used imatinib, which inhibits the PDGF receptors α and β, it remains unclear if combined or selective targeting of the PDGF receptor isoforms is favorable. This issue is even further complicated with imatinib blocking c-Abl and c-Kit. Because of the partially overlapping effects of both receptor isoforms, combined blockade might have superior efficacy. Blocking both isoforms, however, harbors greater risks for side effects. In particular in patients with SSc, inhibition of PDGF-B/PDGFRβ may exacerbate vascular disease complications by interfering with pericyte function.

2.2. VEGF receptors

VEGF signaling shows a similar complexity as the PDGF network. Five different VEGF ligands (VEGF-A, B, C, D and placental growth factor [PLGF]) as well as three different receptors (VEGFR1, 2 and 3) transmit specific signals to modulate downstream information. Of note, splicing variants of VEGF-A can further fine tune VEGF signaling [31]. VEGF-A, -B and PLGF bind to VEGFR1, and VEGF-A is a ligand of VEGFR2. In regard to their biological functions, VEGF-A is a key mediator of angiogenesis and other cellular processes in adults, while VEGF-B is primarily active during embryogenesis. VEGF-C and VEGF-D, but not VEGF-A, are ligands for a third receptor (VEGFR3), stimulating lymphangiogenesis [31]. The VEGFRs are receptor tyrosine kinases with VEGFR2 mediating most of the cellular responses to VEGF to promote vessel formation and vascular integrity [32]. The role of VEGFR1 is more complex: During vasculo- and angiogenesis, VEGFR1 can dampen VEGFR2 responses by trapping VEGF-A or by direct receptor-crosstalk with VEGFR2 [33–35]. In pathological conditions such as ischemia, inflammation, wound healing and cancer, however, VEGFR1 may also synergize with VEGFR2 activity in a PLGF-dependent manner [36].

The link between VEGF signaling and fibrosis may involve direct and indirect mechanisms. Since vascular damage and loss of capillaries are major features in SSc, VEGF signaling is likely to be disturbed. Instead of decreased VEGF signaling as initially suspected, however, VEGF-A levels and VEGFR1 and 2 are strongly up-regulated in SSc skin [37]. This paradox has long been subject of intensive investigations: the first hypotheses assumed that VEGF-driven, angiogenic processes might be futile and even deleterious in SSc, since sufficient tissue angiogenesis depends on strict regulation of VEGF expression [38–40]. In addition, recent experimental evidence demonstrates that anti-angiogenic splicing variants of VEGF-A are selectively overexpressed in SSc, which can impair the formation of functional blood vessels [41]. In particular these recent findings may mark a breakthrough in solving the paradox of severe small-vessel vasculopathy and the—at least seemingly—enhanced vascular response in SSc.

Apart from its central role in SSc vascular disease, there is growing evidence that VEGF/VEGFR signaling has mitogenic and pro-fibrotic effects on fibroblasts. Recent evidence from transgenic mouse models demonstrates that VEGF-A signaling itself can stimulate the production of extracellular matrix proteins [42], providing a potential link between vascular changes and fibrosis in SSc. VEGF-A may also have pro-fibrotic effects in retinal and renal diseases [43–46] in which pathological vascular changes and scar formation are also dominant disease features.

The evidence for a pro-fibrotic role of VEGF signaling, however, is still limited. Future research will need to diligently address the complex VEGF network with its various ligand and receptor subtypes in model systems for different fibrotic diseases. Nevertheless, some of the multi-tyrosine kinase inhibitors already used in clinical trials for fibrotic diseases (as discussed later) also show anti-VEGF activity, which might contribute to their anti-fibrotic activity. Apart from beneficial effects, however, VEGF receptor blockade harbors potential risks, in particular in patients with SSc vasculopathy. Although controlled inhibition of VEGF signaling might counterbalance the overexpression of the VEGF axis to improve SSc vascular disease, complete blockade of VEGF signaling by tyrosine kinase inhibitors could abrogate angiogenesis and worsen vascular disease manifestations. Apart from negative effects on small-vessel vasculopathy, anti-VEGF therapies may increase the risk for renal protein excretion and hypertension [47]. In this regard, interference with VEGF-signaling could hypothetically increase the risk for renal complications in patients with SSc (i.e., renal crisis).

2.3. EGF receptors

EGF ligands bind to a complex system of receptor tyrosine kinases, called the ErbB system. The ErbB system is composed of four membrane-associated proteins, ErbB1 (also known as EGFR), ErbB2 (an orphan receptor), ErbB3 and ErbB4. Apart from EGF, transforming growth factor-α (TGF-α), heparin-binding EGF-like growth factor, amphiregulin, neuregulin, betacellulin, epiregulin and epigen bind to ErbB receptors. Similar to PDGF and VEGF signaling, differential binding of EGF ligands to the ErbBs initiates homodimeric or heterodimeric receptor dimerization to induce autophosphorylation of intracellular kinase domains and downstream cell signaling through mitogen-activated protein (MAP) kinases, phosphatidylinositol 3-kinase (PI3K), and transcription factors including STAT3 [48,49]. Interestingly, EGF receptor may stimulate angiogenesis in tumors by up-regulation of VEGF linking tumor growth with angiogenesis [50]; similar mechanisms may be active in fibrosis, which, however, needs experimental confirmation.

EGF signaling has been implicated into the pathogenesis of pulmonary and renal fibrosis, but only little evidence exists for other fibrotic diseases such as liver fibrosis or skin fibrosis so far [51]. In the lungs, EGF signaling is critical for epithelial–mesenchymal interactions during both healthy states and disease. In this context, EGF signaling acts as an important survival factor for the lung epithelium, but also promotes fibroblast proliferation and extracellular matrix production. In general, the pro-fibrotic effects of EGF signaling appear to be deleterious and promote disease progression in pulmonary fibrosis. Most of the genetic and pharmacological studies indicate that stimulation of EGF signaling exacerbates experimental pulmonary fibrosis, while its inhibition is protective [52–58]. The molecular effects of EGF signaling in pulmonary fibrosis, however, seem to be more complex. Certain EGF ligands, such as amphiregulin, have shown anti-fibrotic effects in models of pulmonary fibrosis [59]. Moreover, EGF ligand—receptor interactions that are otherwise associated with disease progression may show protective effects in certain disease models and states of lung fibrosis. Experimental overexpression of TGF-α, for example, protected mice from nickel-induced lung injury [60,61]. In another study, the selective EGFR inhibitor ZD1839 exacerbated bleomycin-induced pulmonary fibrosis [62]. Of note, approximately 1% of patients with lung cancer receiving the EGFR inhibitors (e.g., gefitinib and erlotinib) develop interstitial lung disease. Risk factors include Asian ethnicity, older age, smoking, preexisting ILD, and concurrent cardiac disease among others [63–65]. Thus, under certain circumstances, targeting of EGF signaling may also worsen fibrosis, which warrants great attention when evaluating EGFR blocking agents in patients suffering from fibrotic diseases.

In renal physiology and pathology, EGF signaling appears to have similar effects as in the lungs, including regulation of epithelial–mesenchymal interactions. Several EGF ligands, such as heparin-binding EGF and TGF-α, are expressed by renal epithelial cells and released after injury. These ligands can bind to EGFR expressed on both renal interstitial fibroblasts

and adrenal epithelial cells [66]. Of note, activation of epithelial EGFR may be involved in renal fibrogenesis, because experimental overexpression of the dominant negative isoform of EGFR in renal tubular cells attenuated the renal fibrotic lesions induced by prolonged renal ischemia and chronic infusion of angiotensin II [67,68]. In renal fibrosis, the pro-fibrotic effects of EGFR signaling may be, at least in part, mediated by TGFβ [69,70]. Finally, genetic or pharmacologic blockade of EGFR can inhibit experimental renal fibrosis [71], suggesting that inhibition of EGFR signaling might be an interesting therapeutic target in the treatment of fibrotic renal disease. Potential protective effects of EGF signaling, as observed in pulmonary fibrosis, have not yet been described for renal fibrosis.

2.4. JAK2 kinases

Janus kinases (JAKs) are receptor-associated tyrosine kinases with central roles in cytokine- and growth factor signaling. The JAK proteins have seven JAK homology (JH) domains [72]. Whereas the JH1 kinase domain phosphorylates target molecules to activate downstream signaling, the JH2 domain is a dual-specificity protein kinase that phosphorylates two negative regulatory sites in JAK2 [73]. The remaining domains (JH3 to JH7) are necessary for protein–protein interactions with cytokine receptors and signal transducers and activators of transcription (STAT) proteins [72]. In analogy to other receptor tyrosine kinases, cytokine binding induces autophosphorylation and activation of JAK kinases [74]. In turn, JAK kinases recruit and phosphorylate STAT proteins. Upon activation, STATs dimerize and translocate into the nucleus where they activate the transcription of several target genes [74]. Apart from the canonical JAK–STAT signaling, a portion of nuclear, unphosphorylated STAT regulates heterochromatin stability, which does not require induction of STAT transcriptional target genes [75].

JAK2 is a key-regulator of cytokine signaling, and alterations of JAK2 signaling cause profound changes in response to cytokine stimulation. Point mutations in the JAK2 gene, which result in constitutive activation of JAK2, are key-events in the pathogenesis of myeloproliferative diseases [74,76,77]. We studied JAK2 in SSc and experimental skin fibrosis. We observed that TGFβ signaling can induce phosphorylation and activation of JAK2, which then interacts with phosphorylated STAT3 to induce fibrotic responses. Interestingly, JAK2 may not only be a downstream target of TGFβ in fibroblasts but also amplify TGFβ signaling by stimulating the expression of TGFβ. In this context, both inhibition of STAT3 and overexpression of SOCS1, an endogenous suppressor of STAT signaling, reduced the expression of TGFβ [78,79]. Finally, inhibition of JAK2 was effective in inhibiting the development of fibrosis in several experimental models, suggesting that JAK2 inhibitors might be promising therapies for patients with fibrotic diseases. As several JAK2 inhibitors are currently evaluated in clinical trials for malignancies and rheumatoid arthritis, the anti-fibrotic effects in experimental models of fibrosis may have direct translational implications.

2.5. c-Abl and c-Kit

c-Abl and c-Kit are non-receptor tyrosine kinases with crucial roles in the development of malignancies. While pathological c-Abl activity is the driving force in CML, activating c-Kit mutations induces and promotes the development of gastro-intestinal stromal tumors (GIST). In CML, a genetic translocation fusing c-Abl to the breakpoint cluster region (bcr) results in permanent activation of c-Abl, which has strong mitogenic effects. Treatment with imatinib can inhibit the pathologic c-Abl activity in CML and induce tumor regression. In the vast majority of gastrointestinal stromal tumors, signaling via c-Kit or PDGF receptors is constitutively activated [80,81], rendering imatinib, which blocks both tyrosine kinases, an effective treatment [82].

Several studies suggest that the anti-fibrotic effects of imatinib and similar small molecule inhibitors, such as nilotinib and dasatinib, are not only mediated by blocking PDGF signaling but also by inhibiting c-Abl and c-Kit. In their landmark work on the anti-fibrotic effects of imatinib in experimental lung fibrosis, Daniels and colleagues suggested that inhibition of c-Abl may be a main mode of action for the anti-fibrotic effects of imatinib. The authors identified c-Abl as a smad-independent downstream target of the pro-fibrotic TGFβ-signaling [27]. We observed that imatinib (as well as nilotinib and dasatinib) inhibited both TGFβ- and PDGF-induced collagen release from fibroblasts [23,25]. Our results are in line with studies in other pro-fibrotic diseases that also suggest a more nuanced situation with anti-fibrotic effects of imatinib and related TKIs mediated by both TGFβ- and PDGF-dependent pathways [26,28,29,83].

The role of c-Kit in fibrosis appears to be even more complex since it is usually expressed in only a few cell types including stem cells, mast cells, melanocytes in the skin and Cajal cells in the intestine [84]. c-Kit activity in mast cells has been linked to different fibrotic conditions [85,86], and some authors suggest that c-Kit might be expressed in fibroblasts during wound healing and tissue fibrosis [87]. Nevertheless, future studies need to confirm these findings and more clearly define the role of c-Kit in fibrosis. This may also help to better dissect the different targets and pathways by which imatinib and similar small molecule inhibitors reduce fibrosis.

2.6. Src kinases

Src kinases, a family of non-receptor tyrosine kinases, are important mediators of pro-fibrotic signaling pathways. For example, Src kinases modulate the activity of TGFβ signaling by phosphorylating and activating TGFβ type II receptor and the downstream target c-Abl [88,89]. Src kinases are activated by increased levels of reactive oxygen species or pro-fibrotic cytokines, including TGFβ, PDGF and angiotensin-2, all of which are present in pro-fibrotic diseases [69,90–92]. The central pro-fibrotic role of Src kinases is confirmed by potent anti-fibrotic effects of the specific Src kinase inhibitor SU6656 in experimental fibrosis [90,93]. Thus, targeting Src kinases may be another promising approach in the treatment of SSc and other fibrotic diseases. Although selective inhibitors of Src kinases are not yet in clinical use, the tyrosine kinase inhibitor dasatinib inhibits Src kinases in pharmacologically relevant concentrations in addition to inhibition of PDGF and c-Abl. A clinical proof-of-concept study with dasatinib in patients with SSc is ongoing.

3. Clinical trials with tyrosine kinase inhibitors in fibrotic diseases—lessons to be learned

3.1. Systemic sclerosis

Effective and tolerable anti-fibrotic therapies are not available in clinical routine but are urgently needed because of the high morbidity and mortality of SSc and other fibrotic diseases. As discussed in the previous sections, results from pre-clinical models suggest that imatinib and similar tyrosine kinase inhibitors (e.g., dasatinib and nilotinib) may have anti-fibrotic effects in SSc [23,25]. Given these preclinical findings and the good tolerability in patients with CML, several clinical trials with imatinib in patients with progressive, diffuse-cutaneous SSc have been performed [94–97]. In these trials, patients received doses of 400 mg up to 600 mg imatinib daily.

At first consideration, the results of these trials are disappointing. Although most of the studies showed a trend towards improvement of skin [94,95,97] and lung fibrosis [95,97], unexpectedly high rates of adverse events led to the withdrawal of imatinib in many patients. The spectrum of adverse effects included edema, fatigue, nausea and vomiting, diarrhea, generalized rash, new onset proteinuria, and muscle weakness, among others. In particular the rate and severity of peripheral edema were unexpected, when compared to the data from the CML trials [98–101], and led to the withdrawal of imatinib in many patients with SSc. Thus, on this first glance, these results might not support the use of imatinib in SSc.

As discussed in a recent editorial by Mendoza and Jimenez, however, a close look at the results of these trials reveals several shortcomings [102]. (i) Effectively all of these trials had a non-controlled design, which does not allow making final conclusions. One study had been designed as a randomized-controlled trial but just included one patient in its placebo group. (ii) Most patients suffered from severe disease including patients with lung involvement and active alveolitis [94,95]. Given the diversity of SSc disease manifestations, most of the spectrum of complications could, at least in part, represent features of SSc rather than adverse events. (iii) Concomitant therapy with methotrexate might have also contributed to the high rates of complications [96].

Because of these limitations, final conclusions of the anti-fibrotic effects of imatinib in patients with SSc are currently impossible. In particular with the high rate of vascular complications, there are concerns that interference of imatinib with PDGF-B/PDGFRβ signaling might further impair pericyte function and vascular repair processes, resulting in exacerbations of SSc vasculopathy with the development of peripheral edema. Of note, the increased rate of peripheral edema might have also confounded the results of the modified Rodnan skin score [103–106], which is the standard primary outcome measure in SSc trials. Peripheral edema can be hard to discriminate from severe skin involvement by SSc, which could lead to increased scoring by skin score.

Thus, many open questions in regard to both efficacy and tolerability of imatinib in SSc remain. In theory, the definite answers may only be found in well-designed, randomized controlled trials. Several obstacles, however, make large randomized-controlled trials in SSc a great challenge: SSc is rare, which makes it difficult to recruit large study cohorts, and SSc can be life-threatening, which raises ethical issues when treating patients with novel agents and placebos in particular over longer periods of time, keeping in mind that few classical DMARDs might have at least marginal positive effects in a subset of patients. Longer treatment periods are necessary, however, when assessing the anti-fibrotic efficacy by the modified Rodnan skin score or by changes in lung function, which are the standard primary outcomes in clinical SSc trials.

Nevertheless, there may be another key to success: we believe that proof-of-concept studies using specific and sensitive fibrosis biomarkers can bridge the gap between early clinical development and large randomized-controlled trials in the future. Fibrosis biomarkers may enable early clinical decision making and help to prevent late clinical failure, in particular those that may respond rapidly to treatment (e.g., changes in protein and mRNA levels of extracellular matrix proteins, or marker genes for key-fibrotic pathways) [107,108]. Nevertheless, these biomarkers still need careful characterization. This approach may also be useful for clinical trials in other fibrotic diseases that face similar hurdles as studies in SSc, including low patient numbers and lack of sensitive and reliable outcome measures. We hope that well-characterized fibrosis biomarkers will help to triage candidate anti-fibrotic therapies and reduce the risk for late clinical failures in the future.

When getting back to the imatinib story, three trials applied fibrosis biomarkers. Our colleagues and we found a reduction of col1a1 and fibronectin mRNA after 6 months of treatment and 6 months of follow-up [3]. Pope et al. observed no change in a rather unselective panel of 25 fibrotic and inflammatory biomarkers isolated from pulverized skin biopsy tissue and plasma samples after 6 months of treatment [5]. Finally, Spiera et al. found that skin thickness decreased during 12 months of imatinib treatment, a marker that might be too insensitive for short-term studies [6]. As preliminary experiences from a proof-of-concept trial with 5HT2B-receptor antagonists suggest, treatment for as short as 3 months (or even shorter) might be sufficient to provide relevant information about the efficacy of novel drugs that directly target fibroblast activation. Knowledge about molecular and pharmacological kinetics suggests that changes on mRNA levels could even be expected within days. To sum up the SSc imatinib trials, the study findings do not suggest a strong anti-fibrotic efficacy of imatinib, but modest anti-fibrotic effects cannot be excluded and might be clinically relevant since effective anti-fibrotic therapies do not exist so far.

3.2. Idiopathic pulmonary fibrosis

In many aspects, the imatinib story in idiopathic pulmonary fibrosis (IPF) resembles closely the one in SSc with many open questions regarding its anti-fibrotic efficacy in patients. Promising results in experimental models of pulmonary fibrosis prompted a double-blind randomized, placebo-controlled trial in 119 patients with IPF. Patients received 600 mg imatinib daily or placebo for a period of up to 96 weeks. The primary outcome was a combined measure of disease progression (defined as >10% decline from baseline FVC) or death, and secondary outcome measures included changes of $Dl_{CO,}$ resting paO_2, 6-minute walk test and health assessment questionnaires among others [109].

Disappointingly, patients treated with imatinib did not show significant improvement in lung function and survival during the follow-up period. Although the primary endpoints were not achieved, imatinib-treated patients showed significantly improved oxygenation at 48 weeks compared with patients receiving placebo. In the last value carried forward analysis, the positive effects on paO_2 were even sustained at 96 weeks. Imatinib was rather well-tolerated by patients with IPF as shown by similar adverse event rates between the treatment and placebo study arms. This contrasts with the high rates of peripheral edema in SSc, and indirectly supports the hypothesis that imatinib might exacerbate vasculopathy in SSc patients and that this may result in significant adverse effects.

The study had several limitations, including a high percentage of patients suffering from only mild or moderate disease, a poorly defined concomitant medication, and an insufficient statistical power. Thus, similar to the situation in SSc, this first negative trial does not preclude further consideration of imatinib and similar tyrosine kinase inhibitors for clinical studies in IPF [110]. Imatinib might still have mild to moderate anti-fibrotic effects in IPF, which might be of clinical relevance in a disease with limited established anti-fibrotic treatment options.

Apart from imatinib, the multi-tyrosine kinase inhibitor nintedanib (BIBF 1120) has recently created a stir in the fibrosis community. Although Richeldi and colleagues formally failed to meet the primary endpoint, too, the results of this large phase II clinical trial with 432 IPF patients are considered promising due to a clear trend for the primary outcome and significant improvements for secondary outcome measures [111,112].

The anti-fibrotic effects of nintedanib that blocks the tyrosine kinases PDGFRα and β, VEGFR1, 2 and 3, as well as FGFR1, 2 and 3 were initially established in models of experimental pulmonary fibrosis [113]. Based on these findings, Richeldi and colleagues studied four different doses of nintedanib or placebo in patients diagnosed with IPF according to published criteria over a treatment period of 12 months. Patients were not allowed to receive IPF-specific therapies other than prednisone up to 15 mg per day on a stable dose. Thus, concomitant treatment with azathioprine, N-acetyl-cysteine, cyclophosphamide or experimental therapies was excluded [111].

In the group with the highest dose of nintedanib (150 mg twice daily), Richeldi and colleagues found a non-significant reduction of 68% in annual decline in FVC compared to the placebo group ($p = 0.06$). The highest dose also resulted in significantly fewer exacerbations and a significant increase in quality of life, both secondary endpoints in this study. The number of adverse events was similar in all groups, but the proportion of serious adverse events appeared to be lowest in the high-dose nintedanib-group. Although generally well-tolerated, the highest dose of nintedanib was associated

with significant side effects, including gastrointestinal symptoms and hepatotoxicity [111].

When compared to imatinib, the nintedanib data are more promising given the positive trend for the primary endpoint and significant findings for several secondary endpoints. These stimulating results have already prompted further phase III studies in patients with IPF, and trials in other fibrotic diseases will likely follow soon. Interestingly, Richeldi and coworkers followed another strategy with a different trial design as we have suggested for future clinical studies in SSc and other rare fibrotic diseases, since the authors bypassed a proof-of-concept trial with blood biomarkers. Lack of validated fibrosis biomarkers in the blood, lung function testing as an objective outcome measure in IPF, and high confidence in the efficacy and tolerability of study medication may have directed the decision for this strategy.

4. Dirty drug or selective inhibitor—what works best?

Fibrosis is an ultimate disease process instigated by different triggers and propelled by various pro-fibrotic pathways. Once initiated, the fibrotic response may persist through several pro-fibrotic pathways that enhance and substitute for each other, even if a single pathway is inhibited. Given the variety of pro-fibrotic triggers and pathways, each fibrotic disease represents itself as a heterogeneous group of disorders. Only few inherited fibrotic diseases, such as the stiff skin syndrome, may have a uniform disease pathogenesis with the activation of a single or few pro-fibrotic signaling cascades.

The results from the nitendanib and imatinib trials in pulmonary fibrosis and SSc suggest that less selective, 'dirty' small molecule inhibitors that target several signaling pathways can be effective in fibrotic diseases, and that their use may not be limited by adverse effects. This therapeutic approach may help to effectively treat a disease spectrum involving different pathologic key events and activation of various pro-fibrotic pathways as found in fibrotic diseases. It may also prevent bypassing of the targeted pro-fibrotic pathways by alternative ones. Simultaneous blockade of several pathways theoretically harbors a greater risk for potential side effects. This may be particularly true in SSc, in which many pathways may have opposing roles in fibrosis and vascular disease. In this context, targeted therapies may have opposite outcomes on disease manifestations with improvement of fibrosis but worsening of vasculopathy, as suspected for the inhibition of PDGF signaling. Thus, simultaneous blockade of several pro-fibrotic pathways may not only show a higher efficacy but also necessitates more careful clinical evaluations in regard to potential side effects.

Classical pharmacology aims to target a molecular pathway involved in the disease as specifically as possible to minimize undesirable side effects. By this selective approach, the risk of unexpected side effects theoretically decreases. Given the clinical, pathological and molecular heterogeneity of most fibrotic diseases, potent anti-fibrotic effects in a broader spectrum of patients, however, may only be achieved if the selected target acts as a core pro-fibrotic pathway or even as a common denominator of several pro-fibrotic signaling cascades.

In the long run, we believe that an increased specificity of anti-fibrotic therapies should be the ultimate goal of translational fibrosis research. To effectively apply these therapies and individualize anti-fibrotic treatment, however, patients with fibrotic disease may need more detailed molecular characterizations. Biomarkers that indicate the activation of certain pro-fibrotic (or inhibition of anti-fibrotic) pathways need to be developed to guide highly specific targeted therapies. In some patients, combinations of several specific targeted therapies may be necessary to achieve treatment goals, while in others, applications of single agents might be sufficient. As long as biomarker techniques to individualize therapy are not well-elaborated, less selective therapies such as the multityrosine kinase inhibitors may be the first choice to effectively treat a spectrum of patients with fibrotic disease. Prior to routine clinical use, however, these therapies need careful preclinical and clinical evaluation to minimize the risks of clinical failure because of a lack of either efficacy or tolerability. In this model, fibrosis biomarkers that are sensitive and specific to detect early changes of the anti-fibrotic activity of candidate agents can help to bridge the gap between preclinical investigations and clinical proof-of-concept studies, both preceding large randomized-controlled clinical trials.

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