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Review

Cancer-associated and non-neoplastic fibrosis: Comparative mechanisms and emerging antifibrotic strategies

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ABSTRACT

Fibrosis is a maladaptive tissue-remodeling process characterized by persistent fibroblast activation, excessive extracellular matrix deposition, and progressive tissue stiffening. Beyond non-neoplastic disorders, fibrosis is also a hallmark of several solid tumors, where it promotes immune evasion, impaired drug delivery, and therapeutic resistance, particularly in pancreatic, hepatocellular, colorectal, and triple-negative breast cancers. In this review, we comparatively analyze fibrosis across non-neoplastic and neoplastic conditions, using idiopathic pulmonary fibrosis as a reference model and comparing it with highly fibrotic tumors. We focus on conserved biological pathways, including TGF-β signaling, ECM remodeling, mechanotransduction, and fibroblast-to-myofibroblast activation, as well as on stromal heterogeneity and the role of cancer-associated fibroblast subsets in tumor progression and immune modulation. We also critically discuss current antifibrotic therapeutic strategies targeting ECM components, fibroblast activation, stromal signaling, and tumor–stroma interactions, highlighting both preclinical rationale and translational limitations. Finally, we examine emerging approaches such as mesenchymal stromal cell-based platforms and drug repurposing strategies bridging oncology and fibrotic diseases. Overall, this review underscores how comparative analysis of cancerous and non-cancerous fibrosis may help identify shared therapeutic vulnerabilities, while supporting the development of context-specific antifibrotic interventions.

1. Background

Fibrosis is a repair process characterized by excessive extracellular matrix (ECM) deposition following tissue injury, resulting from dysregulated wound healing mechanisms. While initially protective, persistent fibrotic remodeling leads to progressive tissue dysfunction across multiple organs. Fibrosis-related diseases – including pulmonary, liver, and myocardial fibrosis, myelofibrosis, and systemic sclerosis – represent a major global health burden and share common biological features despite distinct etiologies [1,2]. In parallel, fibrotic changes are commonly observed as a defining component of the microenvironment of several solid tumors. In highly fibrotic malignancies such as pancreatic, colorectal, hepatocellular, and triple-negative breast cancer (TNBC), stromal expansion contributes to disease progression, immune evasion, and resistance to therapy [3]. In these settings, fibrosis is not merely a bystander process but an active driver of tumor behavior.

Despite extensive research in both fields, fibrosis is commonly approached within disease-specific frameworks, limiting the identification of shared mechanisms and the development of effective antifibrotic strategies. Emerging evidence suggests that conserved biological programs operate across both neoplastic and non-neoplastic conditions [1,4,5], although their functional roles may differ depending on the disease context.

In this review, we provide a comparative analysis of fibrosis across diseases, juxtaposing highly fibrotic tumors and non-neoplastic conditions, using idiopathic pulmonary fibrosis (IPF) as a reference model. By

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focusing on shared mechanisms and context-specific differences, this work aims to identify shared vulnerabilities that could be exploited for the development of future antifibrotic therapeutic strategies.

2. Fibrogenesis across diseases

Fibrosis represents a common pathological endpoint arising from a wide spectrum of triggers, including chronic inflammation (e.g., IPF, viral hepatitis, metabolic dysfunction-associated steatotic liver disease), mechanical injury (e.g., myocardial infarction), environmental exposures (e.g., pneumoconiosis), autoimmune processes (e.g., systemic sclerosis), and tumor-driven signaling [2,6,7]. Despite etiological differences, fibrogenesis is sustained by conserved biological programs across diseases that can be conceptualized as four interconnected steps: initiating triggers, activation of core signaling pathways, engagement of effector cells, and ECM remodeling.

Different exogenous and endogenous stimuli induce tissue damage and the release of pro-inflammatory cytokines, such as transforming growth factor-β (TGF-β), tumor necrosis factor-α (TNF-α), interleukin (IL)−1β, IL−6, and IL−17A, which converge on a set of interconnected signaling pathways [1,8,9]. Among them, TGF-β signaling represents the central regulatory axis, promoting fibroblast activation, myofibroblast differentiation, and ECM production through SMAD-dependent transcriptional programs [10]. This process is further supported by Wnt/β-catenin signaling, where nuclear translocation of β-catenin induces profibrotic gene expression [11]. Additional pathways, including MAPK, JAK/STAT, Notch, Hedgehog, PI3K/mTOR, and connective tissue growth factor (CTGF), further amplify and stabilize the fibrotic response through the regulation of proliferation, differentiation, survival, and inflammatory signaling [12–16].

In parallel, progressive changes in matrix composition and stiffness further sustain disease progression. Enzymatic crosslinking of collagen fibers mediated by lysyl oxidase (LOX), increases matrix rigidity and activates mechanotransduction pathways, including Hippo/YAP/TAZ and Rho/ROCK, further reinforcing the fibrotic phenotype [17–19]. Importantly, these pathways operate as an interconnected network in which cytokine-driven signals and mechanical cues converge at the nuclear level to coordinate gene expression programs sustaining persistent fibrogenesis [19].

Fibroblasts and their activated counterparts, myofibroblasts, are the main effectors of this process (20,21). While myofibroblasts normally undergo apoptosis following physiological tissue repair, during fibrogenesis they remain persistently activated, typically marked by the expression of α-smooth muscle actin (α-SMA) [20], thereby promoting a feedforward loop of ECM deposition and progressive tissue stiffening [21]. In this context, the ECM is a dynamic non-cellular network that not only provides structural support but also regulates tissue homeostasis, including hydration, pH balance, and growth factor availability [22]. As shown in Fig. 1, the ECM consists of two main interconnected components: the basement membrane, that provides structural support through laminin and collagen networks, and the interstitial matrix, that confers tissue hydration and mechanical strength through proteoglycans and fibrous proteins [4]. In fibrotic conditions, both quantitative and qualitative alterations in these components – coupled with increased crosslinking and reduced degradation – lead to matrix stiffening and loss of tissue elasticity, ultimately contributing to organ dysfunction and disease progression [4].

3. Non-cancerous fibrosis: idiopathic pulmonary fibrosis as a reference model

Among non-neoplastic conditions, IPF represents a paradigmatic model of progressive fibrogenesis.

IPF is a rare fibrotic interstitial lung disease that mostly affects men over the age of 60 with a smoking history, with an incidence of 1–13 per 100,000 persons annually and a median survival of 3–5 years [23,24].

Although historically considered a disease of unknown etiology, IPF is now recognized as the result of the interplay of environmental factors and genetic susceptibility. As depicted in Fig. 2, repetitive pulmonary injuries – driven by aging, inhaled particles, and viral agents (e.g., Epstein-Barr virus, cytomegalovirus) [23,25,26] – trigger an inflammatory response characterized by the release of cytokines including TGF-β, TNF-α, IL−1β, and IL−6 [27,28]. In parallel, genetic and epigenetic alterations contribute to disease susceptibility and progression. Genetic variants affecting mucociliary clearance (e.g., MUC5B) [29], telomere maintenance (e.g., telomerase reverse transcriptase) [30], and epithelial integrity (e.g., DSP) [31], together with epigenetic changes such as microRNA dysregulation and aberrant DNA methylation [32],

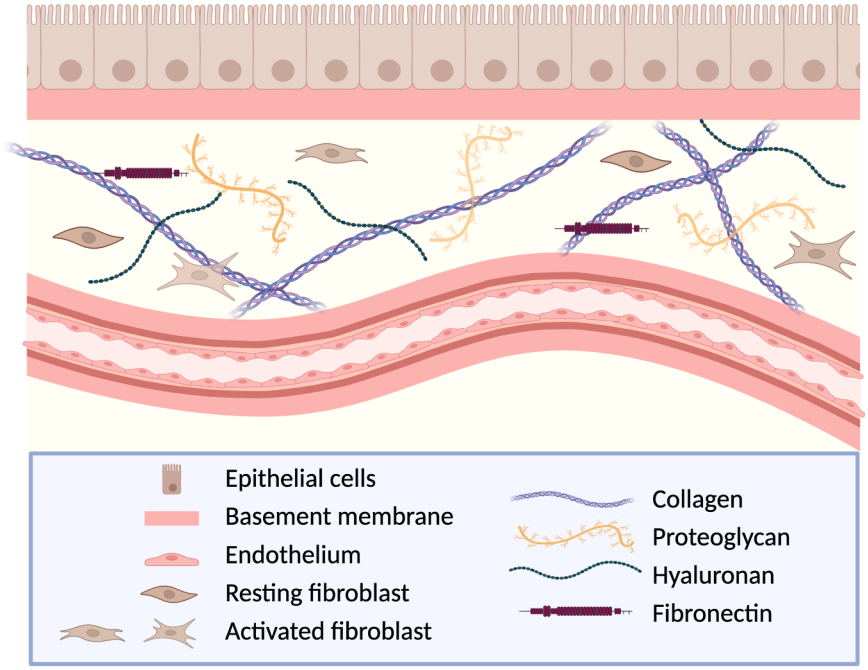

Fig. 1. Composition of the extracellular matrix.

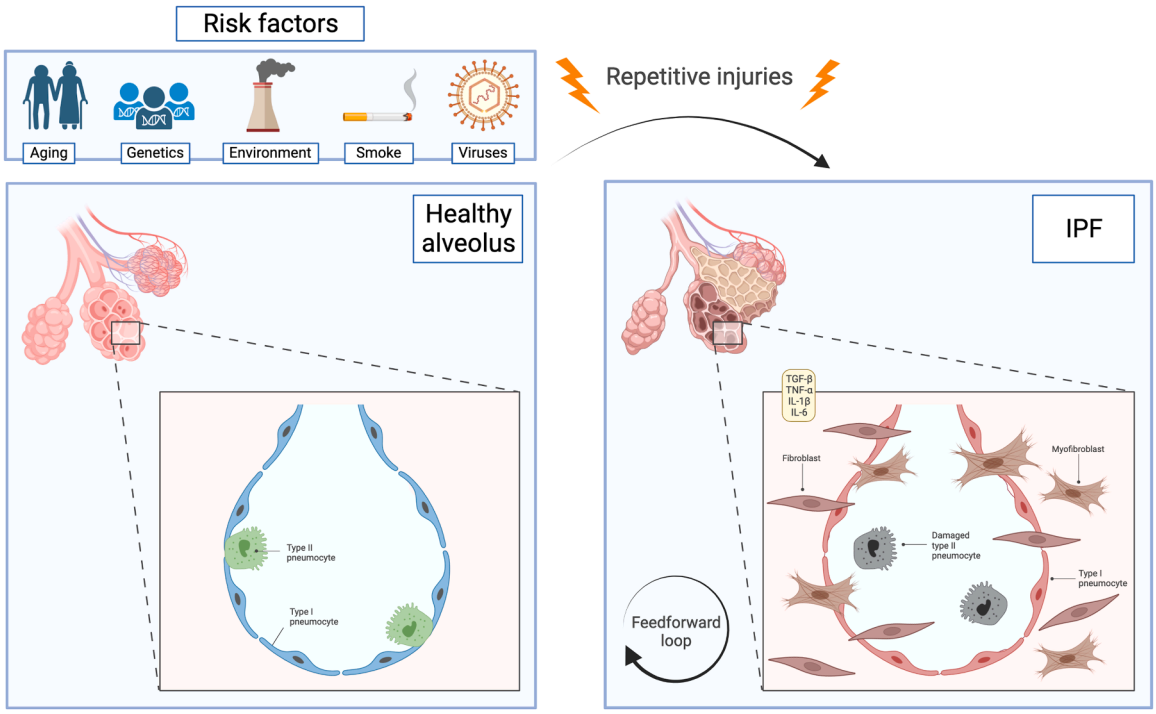

Fig. 2. Pathogenesis of idiopathic pulmonary fibrosis. Abbreviations: IPF, idiopathic pulmonary fibrosis.

promote epithelial dysfunction and impaired tissue homeostasis.

These alterations converge on the activation of the profibrotic signaling pathways described in Section 2, with TGF-β acting as a central driver [33]. The inflammatory process ultimately induces fibroblast-to-myofibroblast differentiation, excessive ECM deposition, and progressive bronchiolization of distal airways. Altogether, these processes establish a self-perpetuating fibrotic circuit in which persistent tissue injury, aberrant repair mechanisms, and progressive mechanical stress ultimately lead to alveolar collapse [27,28].

Notably, several pathogenic mechanisms observed in IPF, including epithelial-mesenchymal transition (EMT) and senescence-associated secretory phenotype development, mirror processes involved in tumorigenesis [33–38]. Consistently, patients with IPF are at increased risk of developing pulmonary malignancies, further supporting the existence of overlapping biological programs [39].

Altogether, these features make IPF a useful reference model to investigate the molecular and mechanical drivers of fibrosis, providing a conceptual framework to interpret fibrogenesis in more complex settings, including cancer.

4. Cancer fibrosis

4.1. Cancer fibrosis development

Cancer fibrosis plays a dual and context-dependent role in cancer biology, since it acts both as a driver of tumor initiation and a hallmark of tumor progression. Many chronic pathological conditions that lead to ECM stiffening (e.g., IPF, chronic pancreatitis, liver fibrosis) are well-known risk factors for tumor development [3]. Conversely, in established malignancies, tumor-driven signaling promotes fibroblast activation and ECM deposition through the release of inflammatory cytokines and the activation of key signaling pathways described in *Section 2*, with TGF-β acting as a central regulatory axis [40]. In the tumor context, however, these pathways are integrated within tumor-stroma interactions that actively promote cancer progression. Inflammatory signaling axes, including NF-κB and JAK/STAT3, play a key role in sustaining cancer-associated fibroblast (CAF) activation and immunosuppression [41,42], while CXCL12-CXCR4 contribute to tumor cell proliferation and immune cell exclusion [43]. In parallel, ECM remodeling and increased matrix stiffness activate mechanotransduction pathways – such as integrin/focal adhesion kinase (FAK), Rho/ROCK, and YAP/TAZ – that reinforce profibrotic signaling and tumor progression [44–46]. Beyond stromal activation, mechanotransduction also promotes loss of epithelial cohesion, facilitating tumor cell detachment and dissemination, a key step in the development of peritoneal carcinomatosis [47].

As shown in Fig. 3, the principal mediators of fibrosis onset and progression are CAFs [48]. Whereas normal fibroblasts are in a resting and non-proliferative state, following inflammatory stimuli, CAFs acquire a contractile, synthetic, and proliferative phenotype, which leads to progressive ECM stiffening and promotes tumor cell dissemination [49–51]. Although CAFs are present in most solid tumors, their abundance varies across tumor types, being particularly enriched in highly fibrotic malignancies, such as pancreatic, colorectal, hepatocellular, and TNBC [52]. Importantly, CAFs are a heterogeneous population that exerts different functional and prognostic roles [53]. Among them, myofibroblastic CAFs (myCAFs) are primarily involved in ECM production, while inflammatory CAFs (iCAFs) display a predominantly inflammatory and immunosuppressive profile [54–56]. Additional subsets, including antigen-presenting CAFs (apCAFs) and FerroCAFs, further highlight the functional complexity of the stromal compartment through their immunomodulatory properties [56–58]. These different CAF subtypes represent functional states along a continuum rather than static entities and their differentiation is shaped by tumor-secreted proteins, such as TGF-β1 for myCAFs and IL−1 for iCAFs differentiation [59]. Beyond CAFs, other stromal components actively contribute to cancer fibrosis. Tissue-specific mesenchymal cells, such as pancreatic stellate cells (PSCs) in PDAC and hepatic stellate cells (HSCs) in HCC, play a major role in ECM production [60,61].

ECM accumulation and remodeling have profound functional consequences, as increased matrix density impairs oxygen diffusion and promotes the stabilization of hypoxia-inducible factors (HIFs), thereby

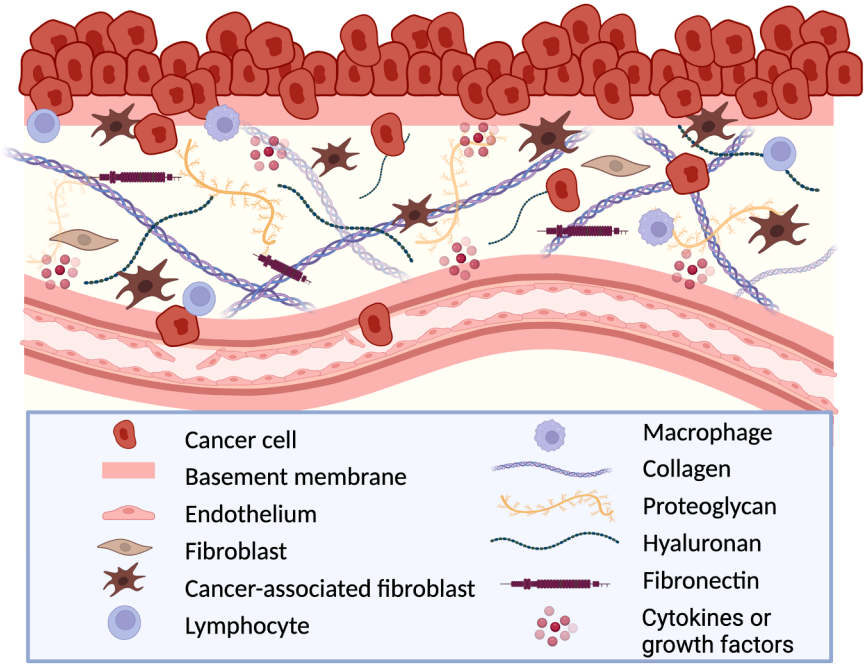

Fig. 3. Extracellular matrix in cancer fibrosis.

inducing the expression of pro-angiogenic factors such as vascular endothelial growth factor (VEGF) and promoting neovascularization [62]. At the same time, the dense ECM structure acts as a physical barrier to immune cell infiltration, impairing anti-tumor immunity [63]. Altogether, these biochemical and mechanical features contribute to treatment resistance and increased cancer aggressiveness.

Taken together, these findings underscore the existence of both recurring and context-specific features across non-neoplastic and cancer-associated fibrosis. A deeper understanding of these convergent and divergent mechanisms may help identify shared therapeutic opportunities and, to facilitate this comparison, the main molecular, cellular, and functional features of IPF and cancer fibrosis are summarized in Table 1.

4.2. *Fibrotic tumors*

The amount and organization of fibrosis differ across tumor types, influencing both tumor biology and clinical behavior. Highly desmoplastic tumors are characterized by a prominent stromal component that actively contributes to disease progression and treatment resistance [50]. In this section, we present key examples of fibrotic tumors, focusing on their distinctive stromal features and clinical implications.

Pancreatic ductal adenocarcinoma (PDAC) is considered the prototypical model of cancer-associated fibrosis, with a dense desmoplastic stroma accounting for up to 80% of the tumor volume [64]. This fibrotic microenvironment is driven by CAFs and PSCs, which activate in response to tumor-derived signals such as TGF-β and platelet-derived growth factor (PDGF), leading to extensive ECM deposition [60,65]. A

Table 1
Comparative overview of fibrogenesis in idiopathic pulmonary fibrosis and fibrotic tumors.

Feature	IPF	Fibrotic tumors
Role of fibrosis	Pathological endpoint, leading to tissue remodeling and organ failure. Increased risk of LC.	Pathological starting point (e.g., HCC) or endpoint in tumor development.
Initiating triggers	Repetitive alveolar epithelial injury driven by aging, smoking, inhaled particles, viruses, and genetic and epigenetic alterations.	Tumor-derived signals, chronic inflammation, pre-existing fibrosis.
Core signaling pathways	Central role of TGF-β/SMAD; activation of Wnt/β-catenin, PI3K/AKT, MAPK, JAK/STAT.	Same conserved pathways integrated with tumor-specific (NF-kB, CXCL12-CXCR4) and mechanotransduction signaling (integrin/FAK, RHO, YAP/TAZ).
Main effector cells	Resident fibroblasts and myofibroblasts.	Heterogeneous CAF populations (e.g., myCAFs, iCAFs, apCAFs, FerroCAFs) and tissue-specific precursors (e.g., PSCs, HSCs).
ECM composition	Progressive deposition of interstitial matrix (collagen, fibronectin, proteoglycans), and altered basement membrane, leading to tissue stiffening and distortion.	Dense and organized ECM, aligned collagen fibers, increased crosslinking, tumor-specific ECM patterns (e.g. periductal in PDAC).
Mechanical consequences	Stiffness leads to fibroblast activation and feedforward fibrogenesis, traction forces induce alveolar collapse and progressive dysfunction.	Stiffness promotes invasion, EMT, loss of cohesion, and immune exclusion.
Hypoxia and vascular effects	Impaired gas exchange due to architectural distortion.	ECM hinders oxygen diffusion, leads to HIF stabilization, and VEGF-driven neoangiogenesis.
Functional consequence	Progressive respiratory failure.	Enhanced tumor progression, metastasis, and treatment resistance.
Immune microenvironment	Chronic inflammation and immune dysregulation.	Immune suppressive TME, CAF-mediated immune modulation.

Abbreviations: IPF, idiopathic pulmonary fibrosis; LC, lung cancer; HCC, hepatocellular carcinoma; CAF, cancer associated fibroblast; myCAFs, myofibroblastic CAFs; iCAFs, inflammatory CAFs; apCAFs, antigen presenting CAFs; PSCs, pancreatic stellate cells; HSCs, hepatic stellate cells; ECM, extracellular matrix; PDAC, pancreatic ductal adenocarcinoma; EMT, epithelial-to-mesenchymal transition; HIF, hypoxia inducible factor; VEGF, vascular endothelial growth factor

defining feature of PDAC is the remarkable abundance and organization of the ECM, characterized by dense, aligned collagen fibers and peculiar periductal distribution [66]. This dense stroma generates a hypoxic and mechanically active microenvironment, contributing to tumor aggressiveness, immune exclusion, and impaired drug penetration [64].

Colorectal cancer (CRC) represents a heterogeneous entity, displaying a variable degree of stromal involvement, with mesenchymal-like tumors characterized by prominent TGF-β activation, stromal infiltration, and poorer clinical outcomes [67]. Beyond its structural role, the stromal architecture also has functional implications: differences in stromal and vascular organization have been linked to variability in response to anti-angiogenic therapies such as bevacizumab, supporting the notion that the fibrotic microenvironment directly influences treatment efficacy [68].

A distinct paradigm is observed in hepatocellular carcinoma (HCC), where fibrosis typically precedes tumor development [69]. Chronic liver injury – driven by viral hepatitis, metabolic dysfunction-associated steatotic liver disease (MASLD), and metabolic dysfunction-associated steatohepatitis (MASH) – induces a continuous cycle of hepatocyte destruction and regeneration, accompanied by activation of HSCs into ECM-producing myofibroblasts [61]. This leads to progressively fibrotic liver tissue, characterized by altered architecture, persistent inflammation, and increasing genomic instability, ultimately favoring HCC development [61]. Clinically, the degree of liver fibrosis is a major determinant of HCC risk, recurrence after treatment, and overall prognosis [70–72]. Although immune checkpoint inhibitors (ICIs) have reshaped the treatment landscape of HCC, most patients develop primary or acquired resistance to immunotherapy [73–75]. In this context, liver fibrosis may contribute to treatment failure by impairing antigen presentation and immune cell trafficking, thereby limiting effective anti-tumor immune responses [76]. In addition, stromal components actively promote immune evasion: CAFs promote immune escape and tumor growth through the secretion of cytokines, chemokines, and other molecules such as prostaglandins and indoleamine 2,3-dioxygenase (IDO), whereas activated HSCs inhibit lymphocyte infiltration and favor the expansion of FOXP3 + regulatory T cells [77–80].

Breast cancer (BC) exhibits subtype-dependent differences in stromal composition, with more aggressive subtypes such as HER2-positive and TNBC displaying a more prominent fibrotic microenvironment [53,81]. Clinically, stromal enrichment is associated with tumor aggressiveness, disease progression, immune suppression, and therapeutic resistance [53,81–84]. In this context, CAF-derived cytokines and growth factors, particularly IL−6 and TGF-β, contribute to EMT induction and reduced sensitivity to chemotherapy and trastuzumab [82–84].

Taken together, these tumor-specific examples highlight that the role of fibrosis in cancer is both context- and time-dependent. In some malignancies, such as HCC, fibrosis precedes and promotes tumor development, partially mirroring the pathogenic sequence observed in IPF, whereas in established tumors it contributes to disease progression, immune evasion, and treatment resistance. Importantly, its functional impact also varies across tumor types: in highly desmoplastic cancers such as PDAC, fibrosis mainly acts as a physical barrier to drug delivery and immune infiltration, while in HCC it exerts a more complex immunomodulatory role that may influence responses to ICIs. Altogether, these observations underscore the need for a deeper understanding of both shared and context-specific mechanisms underlying cancer fibrogenesis.

5. Anti-fibrotic treatment for cancer

Historically, cancer treatment has focused on the direct elimination of tumor cells. However, the increasing understanding of the TME has shifted attention toward the development of novel therapeutics that also consider the non-malignant components. In this context, tumor-associated fibrosis represents an attractive but complex therapeutic target and several strategies are currently being investigated to target different components of the tumor stroma (Fig. 4). Antifibrotic strategies in oncology aim to interfere with the core biological programs driving stromal remodeling, including ECM deposition, fibroblast activation, mechanotransduction, and stromal-immune interactions. In this section, we provide an overview of current and emerging antifibrotic therapies in oncology and, with the aid of Table 2, summarize their biological rationale, current level of evidence, and clinical development status.

5.1. Targeting the ECM

The most intuitive antifibrotic strategy is the **direct targeting of the ECM components**. Among them, hyaluronic acid (HA) has been extensively investigated due to its ability to retain water and increase interstitial pressure, thereby contributing to vascular compression, impaired perfusion, and drug resistance within the TME [126]. Based on this rationale, several approaches have aimed to degrade HA, including the use of PEGylated recombinant human hyaluronidase (PEGPH20) [85,86,126,127]. Other strategies have focused on reducing the stromal density by targeting enzymes involved in ECM remodeling. Members of the lysyl oxidase (LOX) family, such as lysyl oxidase-like 2 (LOXL2), catalyze collagen crosslinking and are frequently upregulated in solid tumors [128]. Accordingly, LOX/LOXL2 inhibition has been explored using agents such as the anti-LOXL2 antibody simtuzumab [89,90]. CTGF is also a potent mediator of EMT, often associated with poor prognosis across tumor types [129–131]. CTGF inhibition has been pursued using agents such as the monoclonal antibody pamrevlumab [91–93].

The ECM can also be targeted by **blocking signaling molecules and pathways** involved in its deposition and maintenance. Several therapeutic strategies have been developed to inhibit the TGF-β pathway [132–134], for instance the angiotensin receptor inhibitor losartan [94–96,135]. Another relevant target is represented by integrins: a family of ubiquitous transmembrane receptors that mediate cell-ECM interactions and activate downstream signaling pathways involved in tumor progression, invasion, and immune evasion [101,136]. Integrin-targeting strategies are being investigated using agents such as ProAgio, an anti-αvβ3 integrin cytotoxin [137]. Downstream of integrins, FAK plays a key role in mechanotransduction and stromal signaling and its inhibition has been explored with agents such as defactinib [138–140]. Finally, Hedgehog inhibitors, including vismodegib and sonidegib, have been investigated for their ability to modulate the tumor stroma and improve drug delivery. Both agents have gained U.S. Food and Drug Administration approval for the treatment of basal cell carcinoma in 2012 and 2015 respectively [99,100,141,142] and have been investigated in PDAC [99,100].

Despite strong preclinical rationale and encouraging early translational results, ECM targeting strategies have failed to demonstrate significant clinical benefit in late stage clinical trials (Table 2).

5.2. Targeting CAFs

Another strategy to attenuate tumor fibrosis involves targeting its main cellular mediators: CAFs. One approach involves the direct **targeting of their surface markers**. Among these, α-SMA is widely used as a marker of activated myofibroblasts and its overexpression correlates with tumor growth and treatment resistance [143,144]. Targeting α-SMA through docetaxel conjugate nanoparticles induced stromal depletion in BC mouse models [106], whereas depletion of α-SMA--positive myofibroblasts in PDAC transgenic mice led to diminished survival [107]. Another marker of fibroblast activation is fibroblast

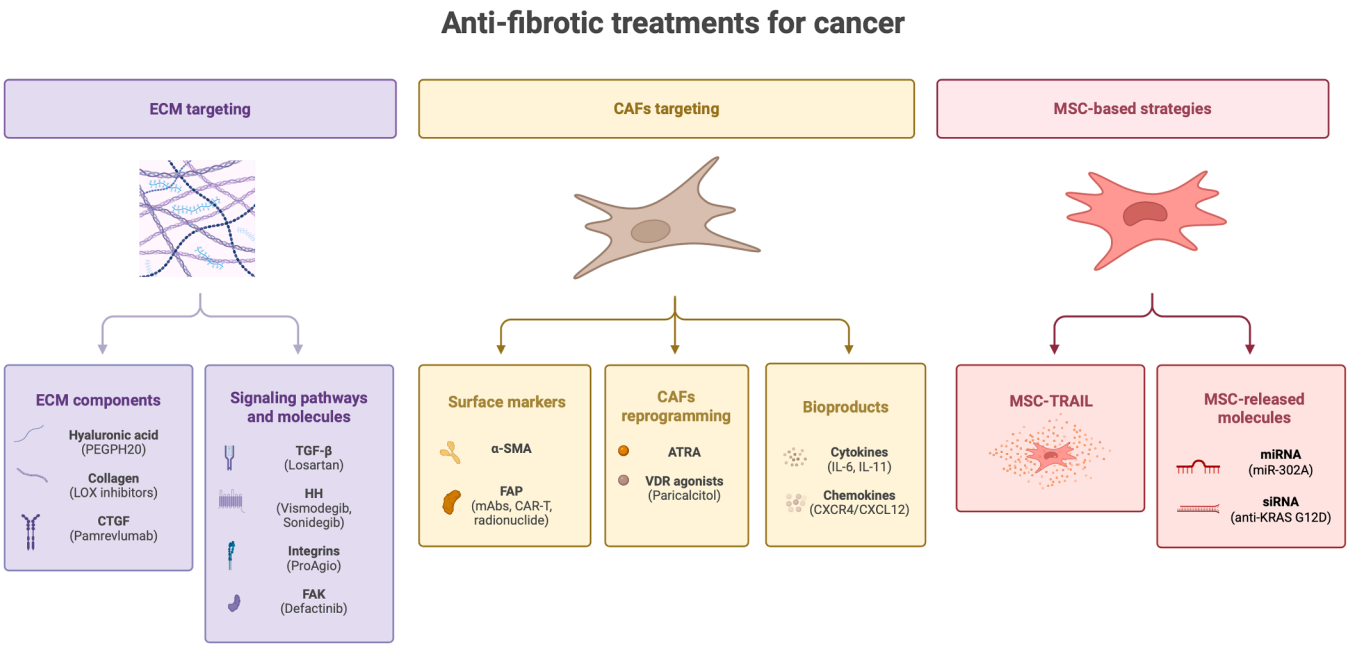

Fig. 4. Antifibrotic treatments for cancer. Abbreviations: ECM, extracellular matrix; LOX, lysyl oxidase; CTGF, connective tissue growth factor; TGFβ, transforming growth factor β; HH, hedgehog; FAK, focal adhesion kinase; α-SMA; α-smooth muscle actin; FAP, fibroblast activation protein; mAbs, monoclonal antibodies; CAR-T, Chimeric Antigen Receptor T-cell; CAFs, cancer-associated fibroblasts; ATRA, all-trans retinoic acid; VDR, vitamin D receptor; MSC mesenchymal stromal cell; TRAIL, tumor necrosis factor-related apoptosis inducing ligand; miRNA, microRNA; siRNA, small interfering RNA.

Table 2
Antifibrotic strategies for cancer.

Strategy	Preclinical support	Highest clinical phase	Drug	Disease setting	Clinical outcome
ECM component targeting					
HA	Improved intra-tumor distribution and efficacy of anti-cancer drugs [85]	Phase III [86]	PEGPH20	PDAC: + gem/nab	Neg
Collagen (LOXL2)	Decreased ECM deposition and tumor growth [87,88]	Phase II [89, 90]	Simtuzumab	PDAC: + gem KRAS mut CRC: + FOLFIRI	Neg
CTGF	Enhanced chemo response in PDAC murine models [91]	Phase III [92, 93]	Pamrevlumab	PDAC: + gem/nab or FOLFIRINOX	Neg
Signaling pathway targeting					
TGF-β	Reduced ECM production, anti-cancer drug delivery and efficacy; TAMs reprogramming to M1 [94,95]	Phase III [96]	Losartan	PDAC: + FOLFIRINOX	Neg
Hedgehog	Enhanced drug penetration and immune infiltration, altered fibroblast composition (increased iCAFs) [97,98]	Phase I [99,100]	Vismodegib Saridegib	PDAC: + gem or FOLFIRINOX	Neg
Integrins	Suppressed tumor cell activity and pro-tumorigenic microenvironment [101,102]	Phase I/II [103]	Abituzumab	KRAS wt CRC: + cetuximab and irinotecan	Neg
FAK	Reduced tumor growth through PI3K/AKT signaling inhibition [104]	Phase II [105]	Defactinib	KRAS mut serous ovarian cancer: + avutometinib	Pos
CAF targeting					
α-SMA	Conflicting results, inducing both anti- and protumorigenic effects [106,107]	NA			
FAP	Antitumor efficacy of various strategies (CAR-T cells, DNA vaccines, immunoconjugates, radioligands) [108–111]	Phase II [112]	^{177}Lu-LNC1004	FAP-expressing advanced solid tumors	Pos
CAF reprogramming					
Retinol restoration	Induced CAFs normalization, reduced Wnt-β-catenin signaling, and cancer cells proliferation [113]	Phase I [114]	ATRA	PDAC: + gem/nab	Pos
VDR	Induced stromal remodeling, enhanced antitumoral activity and chemo effect [115,116]	Phase I [117]	Calcipotriol Paricalcitol	BC: + taxane	Pos
CXCR4/ CXCL12	Improved intratumoral CD8 + T cells and ICI response [118–120]	Phase II [121, 122]	Motixafortide Plerixafor	PDAC CRC	Pos
MSC-based strategies					
MSC-TRAIL	Anti-tumor and anti-stromal activity in combination with gem [123]	NA			
miRNA and siRNA	Suppression of AKT pathway and cyclin D1 expression [124], tumor inhibition and positive immune modulation [125]	NA			

Abbreviations: ECM, extracellular matrix; HA, hyaluronic acid; PEGPH20, PEGylated recombinant human hyaluronidase; PDAC, pancreatic ductal adenocarcinoma; gem/nab, gemcitabine/nab-paclitaxel; neg, negative; LOXL2, lysyl oxidase-like 2; KRAS, Kirsten rat sarcoma virus; mut, mutated; CRC, colorectal cancer; CTGF, connective tissue growth factor; chemo, chemotherapy; TGF-β, transforming growth factor β; TAMs, tumor-associated macrophages; iCAFs, inflammatory cancer-associated fibroblasts; wt, wild type; FAK, focal adhesion kinase; pos, positive; α-SMA, α-smooth muscle actin; FAP, fibroblast activation protein; NA, not available; CAR, chimeric antigen receptor; ATRA, all-trans retinoic acid; VDR, vitamin D receptor; BC, breast cancer; ICI, immune checkpoint inhibitor; MSC, mesenchymal stem cell; TRAIL, Tumor Necrosis Factor-Related Apoptosis Inducing Ligand; miRNA, microRNA; siRNA, small interfering RNA.

activation protein (FAP), a serine protease, whose upregulation is associated with tumor aggressiveness and poor prognosis [145,146] and whose targeting has been explored in the form of DNA vaccines, FAP chimeric antigen receptor (CAR)-T cells, antibodies, and immunoconjugates [108–110,147].

CAF reprogramming also represents a therapeutic option that aims to normalize pro-tumorigenic CAFs into quiescent ones [148]. Based on the knowledge that vitamin A deficiency is linked to fibroblasts activation, restoring retinol reserves induces CAF normalization, downregulation of Wnt/β-catenin signaling, and reduced cancer cell proliferation [113]. In this context, the vitamin A metabolite all-trans retinoic acid (ATRA) has emerged as a potential therapeutic option [114]. CAF activation can also be reversed through agonists of the vitamin D receptor (VDR), a key transcriptional regulator of fibroblast activation [115]. Agents such as calcipotriol and paricalcitol have shown the ability to promote stromal remodeling and enhance chemotherapy efficacy [115–117].

Furthermore, CAFs can be targeted by **blocking their secreted chemokines**, with the CXCL12/CXCR4 axis emerging as a potential therapeutic target due to its central role in fibrosis, where it promotes EMT, immunosuppression, and angiogenesis [149].

Despite the biological rationale supporting CAF-targeting strategies, clinical evidence remains preliminary and heterogeneous. The contrasting results observed with α-SMA targeting highlight the complexity and functional heterogeneity of the stromal compartment, which in some cases may exert tumor-restraining functions [106,107]. Compared with stromal depletion approaches, CAF reprogramming and CXCL12/CXCR4 targeting strategies may preserve the tumor-restraining properties of selected stromal populations while attenuating their pro-tumorigenic functions and are emerging as feasible and safe options in early-phase clinical trials across different tumor types, both alone and in combination with chemotherapy and immunotherapy (Table 2).

5.3. Mesenchymal stromal cells as antifibrotic therapeutic platforms

Mesenchymal stromal cells (MSCs) are multipotent progenitor cells with the ability to differentiate into various cell types, including osteoblasts, adipocytes, and chondrocytes [150]. Owing to their tumor-homing properties, MSCs are increasingly recognized as a potential tool in anti-fibrotic and anti-cancer strategies. In particular, MSCs can serve as delivery platforms for bioactive compounds, including cytokines and chemotherapeutics, through both genetic and non-genetic engineering modifications, allowing selective targeting of the TME [151].

One application relies on MSCs engineered to release the soluble form of Tumor Necrosis Factor-Related Apoptosis Inducing Ligand (TRAIL). TRAIL is an endogenous cytokine that induces cancer cell death by binding to death receptors, which are expressed on both tumor and stromal cells. Interestingly, beyond its antitumor properties, TRAIL has also demonstrated anti-fibrotic activity in preclinical models of lung and liver fibrosis, potentially through the apoptosis of activated fibroblasts or modulation of macrophages and neutrophils [152,153].

Our group has been exploring the use of TRAIL-expressing MSCs for the treatment of several solid tumors, particularly PDAC and sarcoma [154,155] and has recently investigated a combined strategy based on gemcitabine and MSCs engineered to release soluble TRAIL in PDAC models, aiming to target both tumor cells and CAF-rich stroma [123]. This approach significantly affected both tumor growth and stromal remodeling, reducing ECM proteins such as collagen and fibronectin.

Beyond TRAIL delivery, MSCs may also exert therapeutic effects through the release of extracellular vesicles containing bioactive molecules such as microRNAs (miRNAs) and small interfering RNAs (siRNAs), which regulate gene expression and are frequently altered in cancer [156,157].

Although MSC-based therapies have demonstrated favorable safety profiles and encouraging efficacy signals [158], several challenges still limit the clinical implementation of MSC-based therapies. The heterogeneity of MSC donors, sources, isolation procedures, culture conditions, genetic engineering methods, and route of administration significantly affects treatment efficacy and reproducibility [159,160]. Manufacturing consistency, scalability, and standardization of MSC production also represent major barriers for large-scale clinical translation [159,160]. Besides, MSCs may also exert context-dependent protumorigenic effects through immunosuppressive activity, proangiogenic signaling, or support of metastatic dissemination [159,160].

5.4. Future directions

Despite the biological rationale supporting antifibrotic strategies in oncology, their translation into meaningful clinical benefit has proven challenging. Several ECM targeting approaches – including HA degradation, LOX/LOXL and CTGF blockade, and inhibition of integrins and core signaling pathways (e.g., TGF-β and Hedgehog) – failed to improve survival outcomes in clinical trials (Table 2). Possible explanations include stromal heterogeneity, compensatory activation of parallel pathways, and inadequate patient selection. Current research is therefore focusing on optimizing these approaches, for example through the development of pan-LOX inhibitors such as PXS−5505 [161], the αvβ3 integrin cytotoxin ProAgio, and next-generation FAK inhibitors, which are currently under investigation (NCT0508554, NCT05512208, NCT05580445). Other emerging options involve the identification of new targets within pathways and new combinatory strategies, such as the association of the TGF-β inhibitor galuanisertib and nivolumab (NCT02423343).

Direct CAF targeting has also been inconclusive so far and, in certain cases, even detrimental, as for the depletion of α-SMA-positive myofibroblasts in PDAC mouse models [107]. These findings highlight the complexity and context-dependent role of tumor fibrosis, which may exert both tumor-promoting and tumor-restraining functions depending on tumor type, stromal composition, and disease stage. Accordingly, increasing evidence suggests that stromal normalization, rather than complete stromal ablation, may represent a more effective therapeutic paradigm. This concept has supported the development of CAFs reprogramming strategies, which are currently under clinical investigation (NCT04241276, NCT04617067).

The implementation of MSC-based therapies may represent another important step and a phase I/IIa clinical trials assessing the applicability and safety of MSC-TRAIL in locally advanced PDAC is currently underway (NCT06861452). Future research should focus on reducing MSC heterogeneity through source selection and standardized large-scale bioprocessing protocols. In parallel, therapeutic potency could be enhanced through the implementation of genetic engineering and MSC priming approaches. Increasing attention is also being directed toward cell-free approaches, including MSC-derived secretome and conditioned media, which may provide safer, more scalable, and more reproducible therapeutic alternatives [159].

6. Drug repurposing across cancer and fibrotic diseases

The growing recognition of shared biological mechanisms between cancer fibrosis and non-neoplastic fibrotic diseases has opened new opportunities for drug repurposing strategies. Nintedanib – a small molecule tyrosine kinase inhibitor (TKI) targeting vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and fibroblast growth factor receptor (FGFR) – represents one of the earliest examples and has gained regulatory approval for the

treatment of both IPF and lung adenocarcinoma [162,163]. Similarly, the anti-fibrotic pirfenidone, traditionally used to slow lung function decline in IPF patients, demonstrated preclinical activity in TME normalization, EMT suppression, and chemotherapy sensitization in multiple malignancies [164–166]. Notably, retrospective evidence in IPF patients treated with pirfenidone suggest that it might prevent lung cancer occurrence [167]. Based on these findings, two phase I clinical trials are currently evaluating pirfenidone in combination with chemotherapy (NCT03177291) and immunotherapy (NCT04467723) in patients with advanced non-small cell lung cancer.

Beyond currently approved antifibrotic agents, additional compounds with potential applications in both fibrosis and cancer are emerging. Senolytic therapies also represent a promising area of investigation. In particular, the combination of dasatinib and quercetin, a natural flavonoid that inhibits mTOR and PI3K, demonstrated not only feasibility and tolerability in a phase I placebo-controlled study in IPF patients [168], but also anticancer activity in multiple preclinical solid tumor models [169,170]. More recently, the phosphodiesterase 4B (PDE4B) inhibitor nerandomilast demonstrated preclinical antifibrotic activity through downregulation of TGF-β/SMAD signaling [171] and significantly slowed forced vital capacity decline in IPF patients enrolled in the phase III trial FIBRONEER-ILD [172]. Although no direct anticancer evidence is currently available, its effects on stromal and fibroblast-driven signaling suggest a potential future role in modulating tumor-stroma interactions.

Conversely, anticancer drugs may also be repurposed for fibrotic diseases. Preclinical studies underline that the PD−1/PD-L1 axis plays a crucial profibrotic role in IPF [173,174], and analysis on murine models hint that ICI might attenuate fibrosis development [175,176]. Thus, ICIs might represent an area of exploration for IPF treatment. However, given the incidence of ICI-induced interstitial lung disease, the role of anti-PD−1/PD-L1 for IPF patients remains controversial and needs further investigation. Molecular-targeted therapies have also been explored as potential candidates for drug repurposing in fibrotic diseases. Upregulated EGFR expression was found on hyperplastic alveolar epithelium and fibroblasts of IPF patients [177,178] and preclinical data showed efficacy of anti-EGFR therapies in lung fibrosis models [179]. Nonetheless, IPF-associated lung adenocarcinoma appears to be enriched for KRAS, ERBB2, and TP53 alterations, whereas classic oncogenic drivers such as EGFR, ALK, and ROS1 are relatively uncommon [180,181], limiting the applicability of targeted TKIs.

Overall, these findings highlight how the growing understanding of shared fibrotic pathways may foster bidirectional therapeutic repurposing between oncology and fibrotic diseases. Following the example of nintedanib, the expanding landscape of antifibrotic strategies currently under investigation in cancer may also provide new therapeutic opportunities for non-neoplastic fibrotic disorders.

7. Conclusions

Fibrosis represents a shared hallmark across non-neoplastic fibrotic conditions and several solid tumors. Although initiating triggers differ between conditions, convergent mechanisms – including activated signaling pathways, fibroblasts activation, ECM deposition, and immune dysregulation – contribute to tissue disfunction, disease progression, and treatment resistance. These common biological mechanisms provide a rationale for comparing non-neoplastic and cancer-associated fibrosis within a common framework that could have therapeutic implications.

In this context, drug repurposing represents one translational opportunity and nintedanib provides a clinically relevant example of an active compound for both IPF and lung adenocarcinoma. Consistently, many anti-fibrotic drugs are being tested not only in cancer research, but also in other conditions, alone or in combination with pre-existing strategies. The development of such therapeutics is still facing many obstacles, and future research should focus on shedding light on the multiple facets that the stroma holds. A deeper understanding of the diverse CAF subtypes and their phenotypic plasticity, together with the identification of reliable biomarkers, could provide valuable prognostic and therapeutic insights. Likewise, clarifying the downstream signaling cascades triggered by matrix molecules and how cells integrate these cues will be instrumental in refining matrix-directed strategies. Since most current CAF-targeted therapies act primarily on fibroblast growth and behavior, rational combination approaches that integrate stromal, immune, and tumor targeting are needed. Importantly, information about how ECM and stromal cells interact and communicate are still missing. Finally, current research is lacking adequate preclinical models to mimic fibrosis and assess anti-fibrotic drug's efficacy. Novel 2D and 3D platforms, like two-dimensional shear wave elastography and bioprinting technologies, are emerging as non-invasive and reproducible diagnostic and may provide more reliable tools to gain mechanistic insights and test antifibrotic interventions [182,183]. Overall, a pathway-driven and evidence-stratified approach to fibrosis may help transform stromal biology from a descriptive hallmark into a clinically actionable therapeutic target across different diseases.

CRediT authorship contribution statement

Beatrice Riccò: Writing – original draft, Visualization, Conceptualization. **Giulia Grisendi:** Writing – original draft. **Andrea Lo Monaco:** Writing – review & editing. **Dilia Giuggioli:** Writing – review & editing. **Enrico Clini:** Writing – review & editing. **Massimo Dominici:** Writing – original draft, Supervision, Conceptualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Massimo Dominici reports financial support was provided by Dipartimenti Eccellenti MIUR 2022. Massimo Dominici, Giulia Grisendi, Dilia Giuggioli, Enrico Clini reports financial support was provided by European Union - NextGenerationEU. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. The views and opinions expressed are those of the authors only and do not necessarily reflect those of the European Union or the European Commission. Neither the European Union nor the European Commission can be held responsible for them.

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Figures were created in https://BioRender.com.

Data Availability

No data was used for the research described in the article.

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