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Review article

# Activated fibroblasts in cardiac and cancer fibrosis: An overview of analogies and new potential therapeutic options

Giuseppina Nicolini, Silvana Balzan, Francesca Forini *

*CNR Institute of Clinical Physiology, Via G.Moruzzi 1, 56124 Pisa, Italy*

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ABSTRACT

Heart disease and cancer are two major causes of morbidity and mortality in the industrialized countries, and their increasingly recognized connections are shifting the focus from single disease studies to an interdisciplinary approach. Fibroblast-mediated intercellular crosstalk is critically involved in the evolution of both pathologies. In healthy myocardium and in non-cancerous conditions, resident fibroblasts are the main cell source for synthesis of the extracellular matrix (ECM) and important sentinels of tissue integrity. In the setting of myocardial disease or cancer, quiescent fibroblasts activate, respectively, into myofibroblasts (myoFbs) and cancer-associated fibroblasts (CAFs), characterized by increased production of contractile proteins, and by a highly proliferative and secretory phenotype. Although the initial activation of myoFbs/CAFs is an adaptive process to repair the damaged tissue, massive deposition of ECM proteins leads to maladaptive cardiac or cancer fibrosis, a recognized marker of adverse outcome. A better understanding of the key mechanisms orchestrating fibroblast hyperactivity may help developing innovative therapeutic options to restrain myocardial or tumor stiffness and improve patient prognosis. Albeit still unappreciated, the dynamic transition of myocardial and tumor fibroblasts into myoFbs and CAFs shares several common triggers and signaling pathways relevant to TGF-β dependent cascade, metabolic reprogramming, mechanotransduction, secretory properties, and epigenetic regulation, which might lay the foundation for future antifibrotic intervention. Therefore, the aim of this review is to highlight emerging analogies in the molecular signature underlying myoFbs and CAFs activation with the purpose of identifying novel prognostic/diagnostic biomarkers, and to elucidate the potential of drug repositioning strategies to mitigate cardiac/cancer fibrosis.

## 1. Introduction

Heart disease and cancer are the largest contributors to the burden of chronic disease worldwide. Although commonly considered as two separate conditions, these pathologies are frequently intertwined [1]. A growing number of studies confirm the connection between anti-tumor therapy and the cardiac complications. Also, a higher incidence of cancer in association with previous cardiovascular disorders has been documented by several clinical trials and experimental models [2]. Shared risk factors including unhealthy diet, sedentary lifestyle, obesity, diabetes, hypertension, and smoking are critically involved in the pathogenesis of both diseases and are reflected in common cellular processes and signaling cascades [3]. Unraveling such pivotal biological overlap may help to identify novel therapeutic options and preventive strategies for both disorders.

Uncontrolled extracellular matrix (ECM) deposition, resulting in tissue fibrosis, is a common trigger of disease evolution both in adverse myocardial remodeling and in cancer. In the myocardium the cardiac fibroblasts (CFs) represent a highly dynamic cell population embedded within fibrillar ECM, or occasionally near a capillary, and are responsible for the production of the extracellular fibrillar network of the connective tissue. Under physiological conditions, CFs play a central role in maintaining the structural, electrical, and chemical integrity of the heart. In response to injury, such as acute myocardial ischemia (AMI) or pressure overload, CFs are activated into myofibroblasts (myoFbs), a cell type characterized by increased expression of contractile proteins including α-smooth muscle actin (α-SMA) and vimentin that confer a migratory phenotype to facilitate repair and to re-populate damaged tissues [4,5]. MyoFbs can originate also from trans-differentiation of other cell types including endothelial cells, bone marrow-derived circulating progenitor cells, monocytes and fibrocytes [6]. It is now well established that different myoFb phenotypes exist:

* Corresponding author.
*E-mail address:* simona@ifc.cnr.it (F. Forini).

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namely an early post-MI pro-inflammatory phenotype, associated with the secretion of cytokines, chemokines and matrix metalloproteinases (MMPs), and a later post-MI pro-reparative phenotype resulting in the production of anti-inflammatory and pro-angiogenic factors along with ECM components that form the infarct scar [7,8]. When the wound healing process is terminated, a poorly understood STOP signal inhibits the reparative and angiogenic response, myoFb becomes quiescent and may undergo apoptosis [9,10]. However, in the presence of persistent damage, myoFb hyperactivity can result in unrestrained production and deposition of ECM proteins in the myocardium, leading to fibrosis and extracellular stiffness, with detrimental effects on cardiac structure, conductivity, and performance [4].

Similarly to myoFbs, cancer-associated fibroblasts (CAFs) (also known as tumor-associated fibroblasts, carcinogenic-associated fibroblasts, or activated fibroblasts) represent a highly dynamic and abundant cell type within the tumor mass that activates from a quiescent state to a highly proliferative and secretory phenotype to trigger tumor fibrosis via ECM remodeling and cytokine production [11]. Distinct from normal fibroblasts, CAFs exhibit a spindle-shaped morphology with a large, indented nucleus. Regarding α-SMA production, different functional subsets of CAFs have been identified: a high α-SMA-expressing contractile type, termed myCAF, and a low α-SMA expressing non contractile pro-inflammatory type, termed iCAF [12]. Transitions between these two states have also been observed [12]. Like myoFbs, CAFs present significant plasticity and can derive either from resident fibroblasts, or other cell types including pericytes, smooth muscle cells, fibrocytes and mesenchymal stem cells [13]. Together with immune cells, capillaries, and ECM, CAF surround the cancer cells, generating the tumor stroma called tumor microenvironment (TME). As for myocardial fibrosis, the stiffness of the cancer ECM, has increasingly been appreciated as a key factor that not only dictates the TME physical properties, but also fosters malignant transformation and regulates tumor aggressiveness [14–18].

MyoFbs in cardiac injury and CAFs in tumor stroma share similar biological properties and signaling pathways including extensive cell-to-matrix adhesion sites, secretory profile, crosstalk with pro-inflammatory processes and neighboring cardiomyocytes or tumor cells [19,20]. In particular, a reciprocal interplay is established between myoFbs and cardiomyocytes or CAFs and tumor cells by several ways: i) through direct cell contact, ii) indirectly via the extracellular matrix, and iii) by the release of soluble mediators.

In this review we highlight emerging findings on the characteristics and functions of activated fibroblasts in the setting of heart and cancer fibrosis, focusing on their analogies and discussing the therapeutic potential of exploiting the common cascades as druggable targets.

## 2. Role of activated fibroblasts in cardiac and cancer fibrosis

During myocardial disease evolution, the long-lasting activation of fibroblasts into myoFbs shifts the balance of ECM turnover leading to an inappropriate accumulation of connective tissue and maladaptative cardiac fibrosis [21,22]. Few major types of myocardial fibrotic alterations have been described. Reparative fibrosis is evoked to replace a loss of myocardial material following an acute myocardial infarction. In contrast, reactive fibrosis occurs without significant loss of cardiomyocytes, in response to changes in myocardial load or inflammation as observed in hypertension, aortic valve disease, and cardio metabolic disorders [21,23–27]. Depending on the stimulus, reactive fibrosis can develop as a diffuse, disproportionate accumulation of collagen throughout the myocardium (interstitial fibrosis) or involve a more prominent deposition around the intracardiac blood vessels (i.e., perivascular fibrosis).

Besides promoting tissue stiffness, cardiac fibrosis also contributes to slow down the action potential propagation, thus creating re-entry circuits and favoring arrhythmogenesis [28,29]. In addition, interstitial fibrosis observed after MI, in hypertension and in cardiometabolic disease, concurs to cause diastolic dysfunctions [24–27].

In cancer conditions, fibroblasts are activated in CAFs as a result of the crosstalk between tumor cells and stroma and become the dominant cells of the tissue microenvironment [14–17]. CAFs synthesize and modify the extracellular matrix, regulate other cell types in TME via bidirectional cell contact, and release multiple regulatory factors to affect the occurrence and development of cancer in a context-dependent manner.

Initially, CAFs are likely recruited to the tumor to repair the injured tissue and restrain tumor cell invasion. However, as the tumor evolves CAFs continue to deposit ECM proteins moving from a cancer restraining phenotype into a cancer supportive phenotype. The persistent accumulation of cancer cells determines a tissue injury leading to tumor fibrosis characterized by a chronic inflammatory state in which a high numbers of contractile CAFs secrete elevated ECM proteins and enzymes that cross-link and stiffen the matrix [30,31].

High CAF density and altered ECM composition, including an increased ratio between collagen I/III, determine tumor aggressiveness that is associated with poor prognosis [32].

## 3. Common pathways underlying MyoFb and CAF activation

Fibroblast activation and proliferation is a complex process in which several common steps integrate starting from re-shaping of the extracellular microenvironment, followed by signal transduction to the cell nucleus, cell transdifferation and proliferation, and secretion of profibrotic mediators.

### 3.1. Remodeling of extracellular compartment

Increased inflammation and production of reactive oxygen species (ROS) are the first main triggers of profibrotic changes found in the extracellular compartment both in cardiac disease and cancer development (Fig. 1).

For example, in the post AMI setting, myocardial cell death and elevated ROS release lead to lymphocytes and macrophages recruitment in the infarcted and remodeling myocardium. These immune cells secrete specialized matricellular proteins and cytokines, such as Transforming Growth Factor β (TGF-β) and interleukin 10 (IL-10), that activates fibroblasts by binding on surface receptors (see below Section 3.2) [4,5]. Furthermore, cardiomyocytes and vascular cells in the area of injury can also participate in the secretion of profibrotic mediators including cytokines, growth factors, and activators of the Renin-Angiotensin-Aldosterone System (RAAS) [33,34].

Similar to what has been observed for myoFbs, the tissue microenvironment also influences CAF activation. Under local stress, such as hypoxia and oxidative stress, the neighboring tumor cells and the recruited immune cells release growth factors including TGF-β, Platelet-Derived Growth Factor (PDGF), Fibroblast Growth Factor 2 (FGF2), Vascular Endothelial Growth Factor (VEGF), IL6, IL8, Thrombospondin 2, Insulin Like Growth Factor 2 (IGF2) and Insulin Like Growth Factor 1 Receptor (IGF1R) that favor CAF activation and proliferation, production of ECM components, and tumor invasion [35].

### 3.2. Common transduction cascade in MyoFb and CAF activation

The activation of myoFbs/CAFs shares several interconnected transduction cascades that start at plasma membrane receptors upon binding of extracellular factors and culminate in the nuclear modulation of gene expression (Fig. 1). One major route is TGF-β pathway. TGF-β precursor is secreted in the stromal space as an inactive molecule conjugated with the Latency Associated Peptide (LAP), that is cleaved through enzymatic digestion. Mature TGF-β binds to TGF-β type II receptor (TGF-βRII), followed by the recruitment and phosphorylation of TGF-βRI, which leads to the formation of a heterotetrameric complex (Fig. 1). The TGF-β/receptor complex transduces signals through

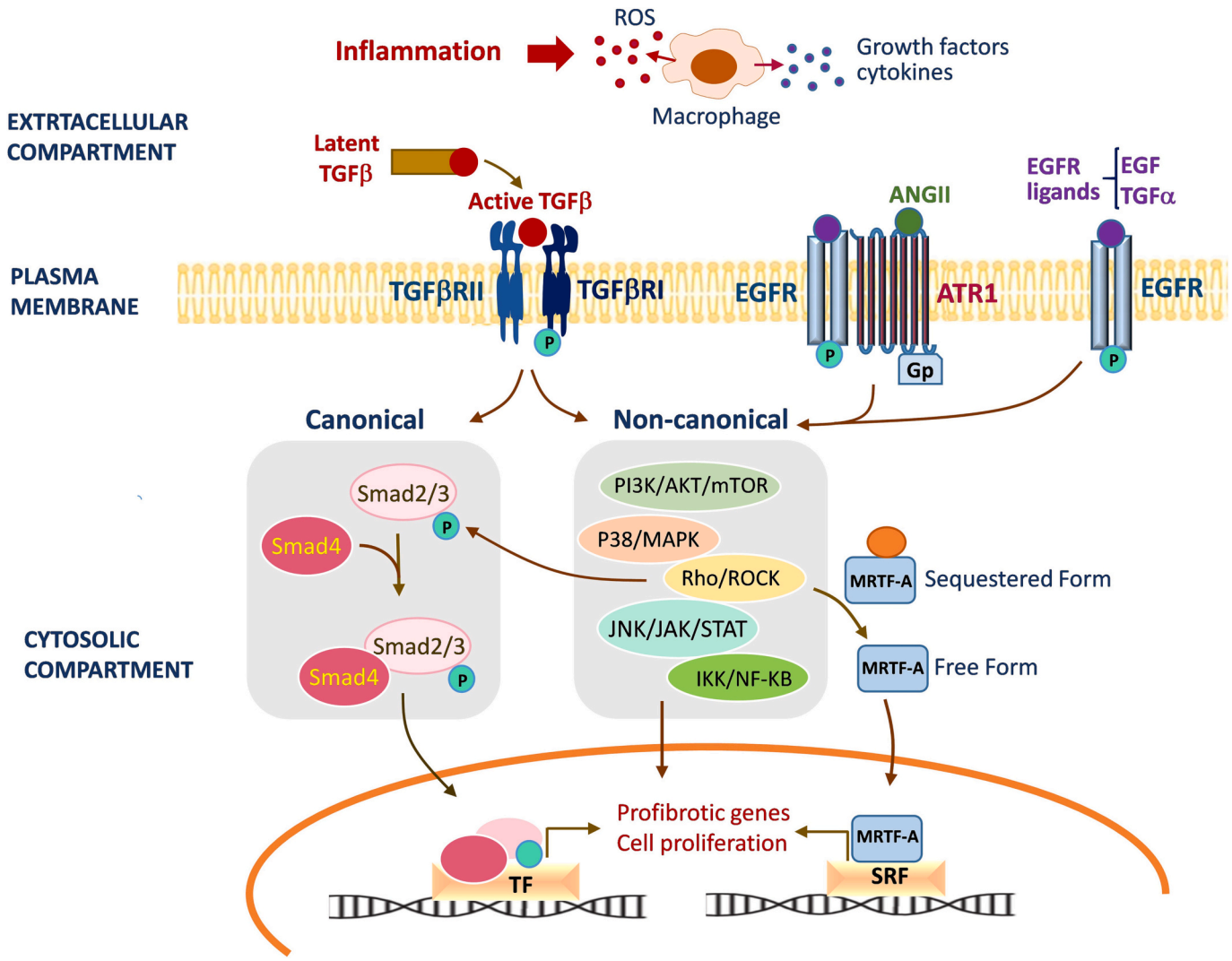


**Fig. 1.** Common processes for fibroblast activation in cardiac and cancer fibrosis. The recruitment of proinflammatory cells, along with increased ROS production and hypoxic conditions, represent the initial steps that shapes extracellular microenvironment. Growth factors and cytokines released from activated macrophages interact with plasma membrane receptors. The signal transduction is accomplished mainly by TGF-β canonical and non-canonical pathways that intersect with other cascades (i.e. EGFR and ATRI) and orchestrate the transcription of a profibrotic and proliferative program. MRTF-A: Myocardin-Related Transcription Factor A; SRF: serum response factor; TF: transcription factors.

canonical and non-canonical pathways. In the canonical pathway, the complex transactivates Mothers Against Decapentaplegic homolog 2 (Smad2) and Smad3 proteins that, upon recruitment of Smad4, move from the cytoplasm into the nucleus to promote the transcription of a profibrotic phenotype [36,37]. This signaling cascade has been observed to favors adverse myocardial remodeling as well as tumorigenesis and metastasis formation [38,39].

The non-canonical TGF-β pathway starts with analogous cytokine processing and formation of tetrameric complex, but intracellular signal transmission is Smad-independent and engages multiple mediators such as: Phosphoinositide 3-Kinase/AKT/Mammalian Target of Rapamycin (PI3K/AKT/mTOR), p38/Mitogen-Activated Protein Kinase (p38/MAPK), Janus Kinase/Signal Transducers and Activators of Transcription (JAK/STAT), IkB Kinase/Nuclear Factor-kB (IKK/NF-kB) and Ras Homolog Family Member A/Rho-associated protein kinase (RhoA/ROCK) [39–41] (Fig. 1). All these circuits converge to the nucleus to regulate TGF-β-mediated transcriptional activity in a context dependent manner.

Other transduction cascades intersect with TGF-β canonical and non-canonical pathways (Fig. 1). One of them starts at the Epidermal Growth Factor Receptor (EGFR) and is involved either in activation of resident fibroblast or transdifferentiation of other precursor cell types. EGFR is a member of the ErbB Receptor Tyrosine Kinases (RTK) family implicated in the transduction of multiple signaling pathways [42]. This transmembrane protein acts as a dimer activated by binding of its specific ligands, including members of epidermal growth factor (EGF) and transforming growth factor α (TGFα). Alternatively, EGFR can be transactivated by recruitment of G-protein coupled receptor upon agonist binding, as in the case of ATR1 and its ligand Ang II [43–45] (Fig. 1). Increased EGFR signaling in fibroblasts has been shown to worsen cardiac fibrosis and is positively correlated with reduced survival in several kinds of cancers [38,46,47].

RhoA and its downstream effector ROCK form another key axis in cardiac fibrosis and in multiple types of solid tumors and are involved in both canonical and non-canonical TGF-β pathways [48]. Rho mediates gene transcription by the downstream Serum Response Factor (SRF) transcription factor and its transcriptional cofactor Myocardin-Related Transcription Factor A (MRTF-A). An increased MRTF/SRF signaling fosters enhanced myoFb and CAF contractility driving adverse cardiac and cancer remodeling [49].

### 3.3. Mechanical regulation of MyoFb/CAF profibrotic phenotype

During fibrosis development, the mechanical forces of the progressive stiffening extracellular compartment promote further activation of myoFbs and CAFs, thus forming a positive feedback loop that accelerates fibrotic tissue deposition [50,51]. Therefore, a better understanding of the transduction pathways in response to a stiffened matrix could offer interesting therapeutic insights. The connections established between the ECM and the cytoskeleton are responsible for the conversion of mechanical stimuli of the stroma microenvironment in biochemical information within the fibroblast cells (Fig. 2).

The mechanotransduction occurs mainly through transmembrane mechanoreceptors belonging to the integrin focal adhesion protein family [52,53]. While physiological integrin activation is required for the normal functionality of cell adhesion, migration and extracellular matrix assembly, aberrant integrin-mediated mechanical signaling plays a key role in adverse cardiac remodeling and cancer. Interestingly, the transmission of mechanical forces through integrins αvβ3, αvβ5, αvβ6, and αvβ8 has been suggested to contribute to the activation of latent TGF-β1 through conformational changes that favors the cleavage of the LAP and promote the transcription of a profibrotic phenotype [52,53].

Besides integrins, other plasma membrane components have been implicated in mechanoreception including syndecans, selectins, cadherins, G-protein coupled receptors, tyrosine kinase receptors, ion channels, lipid rafts and glycocalyx [54–57] (Fig. 2). For example, in cardiac fibrosis, the Transient Receptor Potential Cation Channels 4 (TRPV4) represents a non-selective calcium-permeable cation channel that has been shown to play a key role in mechanosensing and myoFbs activation by integrating mechanical and soluble signals [58,59] (Fig. 2). Although the role of TRPV4 in the activation of CAFs is less well characterized, the available evidence suggest that it may be an important player in tumor fibrosis via sensing the mechanical properties of the tumor stroma [60]. Other extensively studied mechanotransducers in mammalian fibroblasts are Yes-Associated Protein (YAP) and its homologous protein Transcriptional Co-Activator With PDZ-Binding Motif (TAZ). YAP/TAZ are localized mainly in the cytoplasmic compartment where they transduce the structural and mechanical features of the cell microenvironment to the transcriptional machinery of the nucleus. Of note, YAP and TAZ play important roles in various types of fibrosis through the interaction with several mechanosensory proteins such as

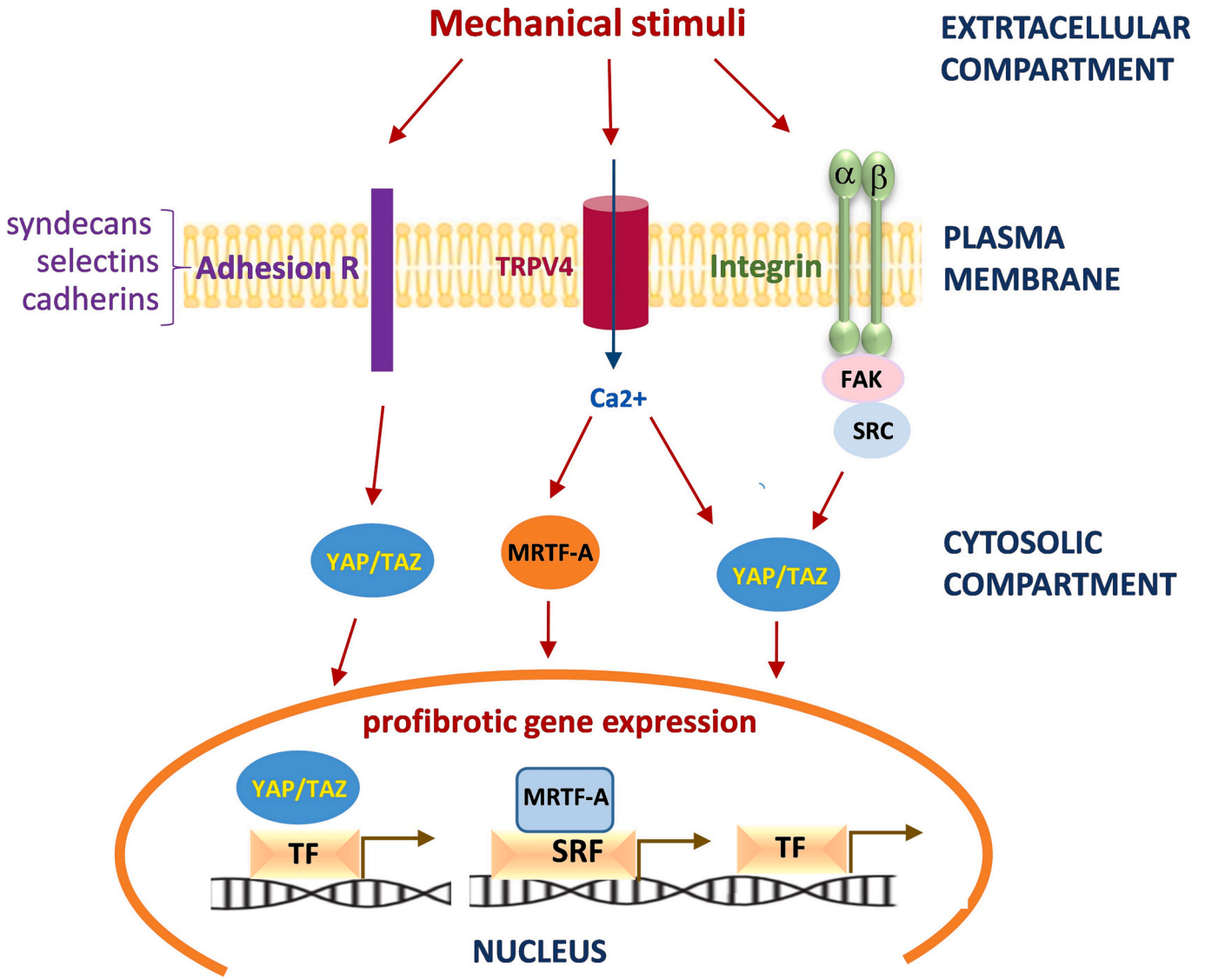


**Fig. 2.** Common mechanical transduction signaling for fibroblast activation in cardiac and cancer fibrosis. The mechanical stimuli of the extracellular compartment are sensed by the plasma membrane receptors (integrins, adhesion receptors or Transient Receptor Potential Cation Channels 4) and transduced to the nucleus via several cascades including: YAP/TAZ (Yes Associated Protein/Transcriptional co-activator with PDZ-binding motif), MRTF (Myocardin-Related Transcription Factor A), and FAK/SRC (Focal Adhesion Kinase/Steroid Receptor Coactivator).

vinculin and talins, as well as the Focal Adhesion Kinase (FAK), Steroid Receptor Coactivator (SRC)-kinase, and G-Protein-Coupled Receptors (GPCRs) [61–63] (Fig. 2). In addition, YAP and TAZ can also translocate to the nucleus and act as transcriptional co-activators to induce the expression of cell-proliferative and anti-apoptotic genes [62]. In cardiac fibroblasts the abrogation of the YAP/TAZ pathways attenuates adverse remodeling and stiffness under cardiac injury by modulating fibroblast proliferation, activation to myoFbs, and the production of fibrotic cytokine [64–66]; while in CAFs increased matrix stiffness have been found to enhance YAP/TAZ signaling activation [67,68].

### 3.4. Metabolic reprogramming

Another main feature of fibroblast activation, observed both in cardiac disease and cancer progression, is the so called "Warburg Effect". First described in cancer cells, this phenomenon consists in a metabolic reprogramming with increased aerobic glycolysis and lactate production in the presence of sufficient oxygen to support mitochondrial oxidative phosphorylation. To confirm the adverse effect of such a metabolic shift, glycolysis inhibition in a rat model of myocardial infarction alleviates cardiac fibrosis by suppressing fibroblast activation [69]. Even though the underlying mechanisms are still unknown, several papers on other types of tissue fibrosis, including renal fibrosis and lung fibrosis, indicate a critical role of the increased lactate production and TGF-β signaling in favoring fibroblast differentiation (see ref. [41] for a comprehensive review). Indeed, the activation of latent TGF-β in the stroma is driven by a low pH environment and is controlled by the Hypoxia Inducible Factor 1 alpha (HIF1α) [70]. Given the pivotal role of HIF1α as a master regulator of the hypoxic response, the hypothesis that accumulation of tissue lactate under hypoxia conditions may trigger cardiac fibroblast differentiation is noteworthy and warrants further investigation.

When tumor development is concerned, TGF-β, PDGF and ROS secreted by cancer cells induce a metabolic shifts in neighboring CAFs, consisting in increased glucose uptake and glycolysis even in the presence of oxygen and well-functioning mitochondria [71]. Through this process, CAFs produce high levels of energy rich 'fuels' (i.e. pyruvate, ketone bodies, and lactic acid) that feed cancer cells, thus increasing their proliferative ability. Such metabolite transfer is known as reverse Warburg effect [72]. The role of HIF1α accumulation in enhancing the glycolytic flux in CAFs and cancer cells is well established. Besides that, increasing evidence suggest that the downregulation of two caveolins, i.e. CD36 and Caveolin 1 (CAV1), drive the metabolic reprogramming of CAFs leading to a local stromal accumulation of mitochondrial fuels [73–75]. Also, the autophagy substrate and signaling adaptor p62 has recently emerged as a critical regulator of CAF biology in many types of solid tumors [76,77]. Reduced p62 levels, triggered by cancer cell-derived lactate, promote tumorigenesis through CAF activation and metabolic reprogramming [78]. For example, in several tumors of epithelial origin, the downregulation of p62 in the stroma leads to an upregulation of the Activating Transcription Factor 4 (ATF4) cascade that results in asparagine generation as a source of nitrogen for stroma and cancer cell proliferation [79].

### 3.5. Secretory proteins

With respect to quiescent fibroblasts, myoFbs and CAFs show an altered secretory profile [79–81]. Both cell types secrete high levels of ECM proteins including collagen, fibronectin and tenascin-c that play a major role in generation of tissue fibrosis and in matrix stiffening observed in cardiac and tumor disease [81–85]. Of relevance to ECM remodeling, myoFbs and CAFs also secrete proteolytic enzymes such as MMPs that are responsible of the ECM degradation [67,86,87]. Specifically, MMP2, MMP3 and MMP9 degrade the basement membrane to initiate cancer cell invasion and metastasis [88,89] or to regulate the abundance of interstitial collagen isoforms (initially type III and later, during the infarct healing, type I), which is crucial for increasing tensile strength and preventing heart ventricular wall rupture [90]. Also, myoFbs/CAFs secrete Lysyl Oxidase (LOX) enzymes. LOX have been identified as downstream targets of the ROCK/actin/MRTF/SRF profibrotic signaling pathway [91]. In cardiac fibrosis an increased LOX contribute to determine left ventricular stiffness and heart dysfunction [92–94], while in solid tumors, increased expression of LOX by CAFs favors matrix and collagen cross-linking in the extra-cellular compartment, thus remodeling the stroma architecture [95–97]. Finally, both cell types produce high amounts of pro-inflammatory cytokines and growth factors. Notably, the fibroblast-derived TGF-β plays a principal role in cardiac and cancer fibrosis. Other relevant secretory proteins are VEGF, IL-6, and CXC-chemokine ligand 2 (CXCL2), that stimulate the proliferation and infiltration of endothelial cells to promote abnormal angiogenesis in cardiac disease, or to favor tumor survival [81–84].

## 4. Regulation of MyFb/CaF activity by microRNAs

Non-coding RNA molecules are increasingly recognized as critical regulators of almost all physiological processes during development and in mature tissue and organs; as a consequence, their aberrant expression has been implicated in a wide variety of pathological conditions including the adverse profibrotic remodeling observed in cardiac disease and cancer. In accordance with the shared signaling pathways that promote fibroblast activation in myocardial tissue and tumor microenvironment, similitudes can also be found in the signature of differentially expressed non-coding RNAs in the two pathological conditions (Table 1).

MicroRNAs (miRs) are the most widely investigated non-coding RNA species, acting as negative regulators of gene expression by inhibiting mRNA translation or promoting mRNA degradation [98]. According to accumulating evidence, several miRNAs, that are downregulated in cardiac fibrosis, such as miR-29, miR-1, miR-26b, miR-205, and miR-338, could play a potential antifibrotic role by targeting genes coding for profibrotic factors in myoFbs including: TGF-β1, TGFβR1, SMAD2, SMAD3, and JAK [39,99,100] (Table 1). Specifically, overexpression of cardiac miR-29b was able to blunt Ang II-induced cardiac fibrosis and to improve cardiac performance by inhibiting the TGFβ/Smad3 pathway [101]. MiRNA-1, a significantly repressed miRNA upon fibroblast activation, is a novel negative regulator of adult cardiac fibroblast proliferation by targeting two cell cycle regulators: Cyclin D2 and cyclin-

**Table 1**
Dysregulated miRNAs in cardiac and cancer fibrosis.

| Downregulated antifibrotic miRNAs | | |
|---|---|---|
| miRNA | myoFb<br>Target gene/signaling | CAF<br>Target gene/signaling |
| 29 | TGF-β/SMAD3 (Ref [101]) | CCL11, CXCL14 (Ref. [114,116]) |
| 1 | CCND2, CDK6 (Ref. [102]) | CCL2/VEGFA (Ref. [113,115])<br>GLIS1 (Ref. [121,123]) |
| 26b | COL1A2, CTGF (Ref. [103]) | TNKS1BP1, CPSF7, COL12A1 (Ref. [115,117]) |
| 205 | P4HA3 (Ref. [104]) | YAP1/STAT3 (Ref. [116,118]) |
| 338 | FGFR2 (Ref. [106]) | c-FOS, cyclin D1(Ref. [122,124]) |

| Upregulated profibrotic miRNAs | | |
|---|---|---|
| miRNA | myoFb<br>Target gene/signaling | CAF<br>Target gene/signaling |
| 21 | SPROUTY/MAPK (Ref. [108])<br>MMP (Ref. [112]) | TGF-β (Ref. [125])<br>Smad7 (Ref. [126])<br>Warburg effect (Ref. [127]) |
| 34a | TGF-β/Smad4 (Ref. [107]) | TP53. (Ref. [119]) |
| 125b | TP53, Apelin (Ref. [110]) | TP53 (Ref. [128]) |
| 155 | TGF-β/Smad3 (Ref. [111]) | P53 (Ref. [129])<br>SOC1 (Ref. [130]) |

dependent kinase 6 [100,102]. In the diabetic mouse myocardium and in Ang II-stimulated mouse CF miR-26b-5p exerted antifibrotic effects by targeting Col1a2 and connective tissue growth factor (CTGF) [103]. Again, miR-205 was found to be downregulated in a rat model of Ang II-induced atrial fibrosis, while its overexpression inhibited fibroblast proliferation and migration by targeting the subunit alpha 3 of Prolyl 4-Hydroxylase (P4HA3) [104]. Even though the precise function of this P4HA isoform remains unclear, it seems to facilitate Ang II-dependent atrial fibrosis [104]. Similarly, the expression of the antifibrotic miR-338 was repressed both in animal models of myocardial ischemia/reperfusion and heart failure, and in patients with dilated cardiomyopathy [105,106]. In detail, the work by Huang et al. in a mouse model of cardiac overload provides evidence that miR-338-3p suppresses cardiac fibroblast activation, proliferation, and migration by directly targeting FGFR2, and may serve as a prognostic biomarker of dilated cardiomyopathy [106].

Conversely, other miRNAs, such as miR-21, miR-34a, miR-125, and miR-155 that are upregulated in myoFbs, favor cardiac fibrosis [109,111] (Table 1). The increased miR-21 expression in myoFbs exerts a profibrotic action by targeting Sprouty homolog, a negative regulator of the MAPK, or by repressing MMP2 inhibitors, as observed in failing murine hearts and in myocardial ischemia-reperfusion respectively [107,112]. In model of cardiac ischemia, miR-34a plays a critical role in fibroblast activation and progression of cardiac tissue fibrosis by directly targeting Smad4 [113]. MiR-125b is induced in both fibrotic human heart and murine models of cardiac fibrosis. As revealed by RNA-sequencing analysis, miR-125b is a core component of fibrogenesis in the heart by altering the gene expression profiles of key fibrosis-related genes. Experimental findings indicate that miR-125b is necessary and sufficient for the induction of fibroblast proliferation and fibroblast to myoFb transition by functionally targeting p53 and apelin, critical repressors of cell proliferation and fibrogenesis [110]. Finally, miR-155 has been shown to promote fibroblast activity and cardiac fibrosis by enhancing TGF-β signaling and glucose utilization in myoFb [111].

A similar set of miRNAs is also differently expressed in cancer tissues as reported by wide genome screenings [114]. Downpregulation of miR-29, miR-1, miR-26b, miR-205, and upregulation of members of miR-34 family could transform resident fibroblasts into CAFs [113–119] (Table 1). The lack of miR-29 in CAFs promotes cellular viability and metastasis of breast cancer by upregulating the expression of CCL11 and CXCL14 chemokines and by activating p38-STAT1 [116]. The tumor suppressor miR-1 has been found to be downregulated in several solid tumors both in cancer cells and in CAFs [120,121]. Although the antifibrotic role of the miRNA in cancer development still awaits to be explored in detail, experimental inhibition of miR-1 contributes to the activation of normal fibroblast into CAFs [115]. Also, the available evidence, suggests that a reduced secretion of miR-1 by activated tumor fibroblasts could abrogate the protective paracrine effects of miR-1 against proliferation and chemoresistance as observed in lung and breast cancer cells [112,123]. A reduction of miR-26b and miR-205 in breast cancer fibroblasts is responsible respectively for increased production of Col12 (a matrix component) and for CAF activation via YAP1 signaling [117,118]. Lastly, miR-338-3p, a tumor suppressor found to be downregulated in tumor progression, has recently been shown to abrogate estrogen mediated cell proliferation of CAFs and breast cancer cells by inhibiting the expression of c-FOS and cyclin D1, two important triggers of cell cycle progression [124].

Among the profibrotic miRNAs, upregulation of miR-21 has been found in CAFs of several tumors such as lung adenocarcinoma, breast cancer and pancreatic cancer [125–127]. Notably, miR-21 promotes tumor progression by mediating the Warburg effect in CAFs [114,127]. In some instances, cancer cell-derived miRNAs exert paracrine effects to induce the phenotypical switch of resident fibroblasts. For example, breast cancer cell-derived extracellular vesicles enriched in miR-125b reprogram quiescent fibroblasts through inhibition of the p53 pathway [128]. Similarly, melanoma and pancreatic cancer cells release exosomes containing miR-155, which promote the conversion of normal fibroblasts in profibrotic and proangiogenic CAFs by targeting p53 cascade and the Suppressor Of Cytokine Signaling 1 (SOCS1) [128,130].

## 5. Drugs against MyoFb/CAF

In the light of the above evidence, mitigating cardiac/cancer fibrosis by targeting myoFb/CAF activation cascades offers numerous promising therapeutic strategies for fibrosis-associated heart/cancer disease [131,132]. At the moment some targets of cascades co-present in myoFb/CAF activation have been identified as common therapy, in some cases just verified in humans, and in other cases only in experimental models. The therapeutic interventions under consideration include both agents specifically developed with an antifibrotic purposes and repositioning of long used drugs [133,134] (Fig. 3).

### 5.1. Inhibitors of TGF-β signaling

Giving the critical role of TGF-β as common mediator of cardiac fibrosis and cancer progression, inhibition of TGF-β signaling is regarded as intriguing strategy for the treatment of myocardial fibrosis and cancers [131,132]. Clinical and experimental studies have shown that for numerous drugs created for various, non-antifibrotic purposes, the benefit could be, at least partially, linked to their antifibrotic effects. Here we report some promising antifibrotic drugs that could be re-proposed to improve therapies in cardiac and cancer fibrosis.

#### 5.1.1. Sartans

Sartans are antihypertensive pharmaceutical compounds primarily developed to inhibit the activity of the RAAS system. In the cardiovascular field, treatments with angiotensin-converting enzyme inhibitors and AT1 blockers have shown to be protective against the development of heart failure, which is dependent on reduced myoFb activation and cardiac fibrosis [135].

When considered in the oncology field, RAAS inhibitors have been shown to reduce the synthesis of collagen and hyaluronan by hampering the TGF-β1 signaling [136,137]. The selective AT1R blocker (ARB), losartan, has been found to attenuate the TGF-β dependent CAF activation, and to reduce α-SMA expression [136]. One proposed molecular mechanism is the inhibition of the Ang II-mediated synthesis of thrombospondin, a major activator of TGF-β [138,139]. Also, by decompressing the tumor stroma and blood vessels, angiotensin inhibition enhances drug delivery, potentiates chemotherapy, and improves tumor response to radiation [136].

#### 5.1.2. Vitamin D and Retinoic Acid

Vitamin D receptors (VDR) are widespread in cardiovascular system and the liganded VDR may play an important role in controlling cardiac fibrosis. It has long been recognized that 1,25-dihydroxyvitamin $D_3$, the biologically active form of vitamin D, can affect myocardial ECM homeostasis via interfering with the expression of MMPs, and tissue inhibitors of metalloproteinases (TIMPs) [140–142]. More recently vitamin D has been shown to prevent TGF-β1-mediated biochemical and functional profibrotic changes in human primary cardiac fibroblasts and to successfully improve cardiac function and alleviate myocardial fibrosis via downregulating TGF-β1 and Smad2/3 signaling in a rat model of myocardial infarction [143,144]. In the clinical arena, an inverse relationship between vitamin D status and cardiac fibrosis has been observed in patients with end stage heart failure [143].

Deficiency of vitamin D is also common among cancer patients [145]. However, studies on the action of vitamin D on tumor stromal cells are still scarce. The available experimental evidence suggests that suppressing TGF-β-Smad2/3 signaling via treatment with VDR ligands could attenuate the differentiation of stellate cells in profibrotic CAF, thus interfering with the tumor promoting secretome in liver and pancreatic tumor stroma [144–148].

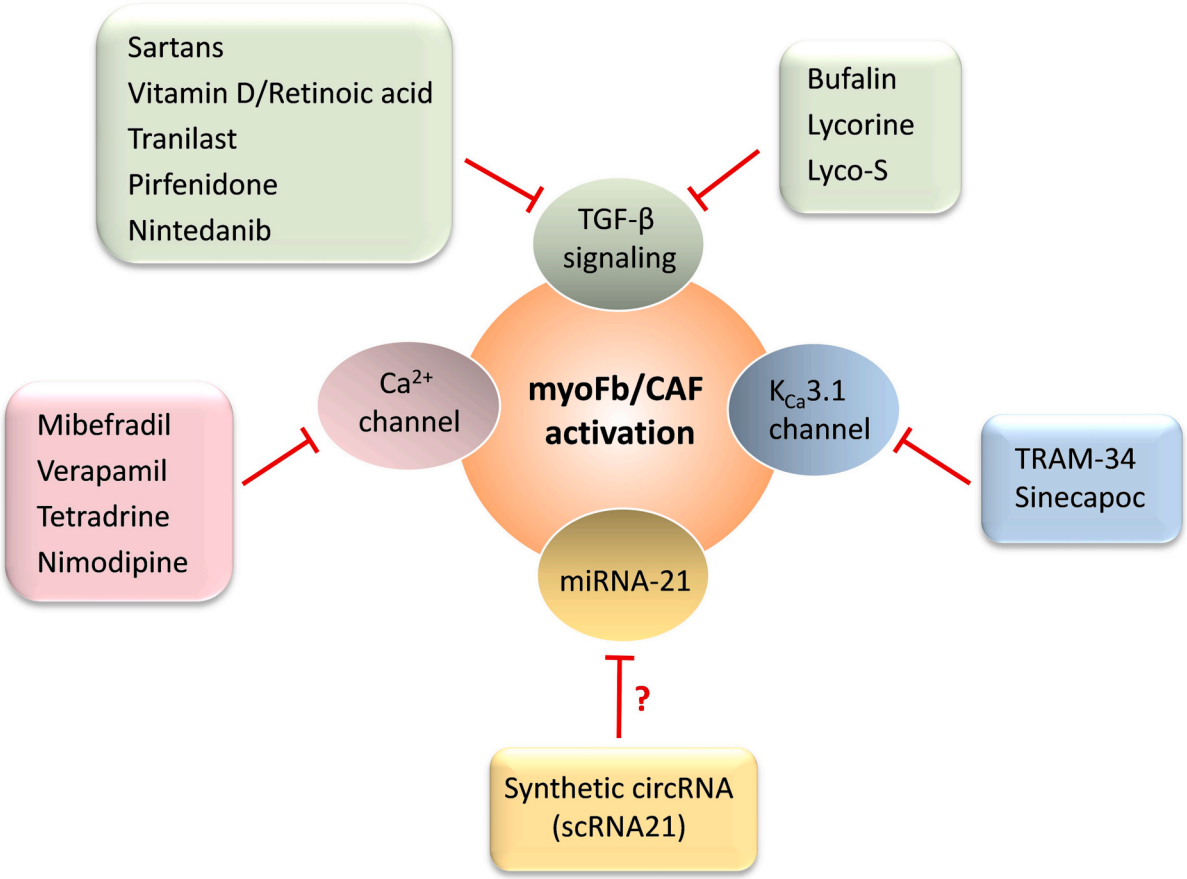


**Fig. 3.** Therapeutic strategies to limit cardiac and cancer fibrosis. KCa3.1: calcium activated potassium channel 3.1; Lyco-S: analogue of lycorine compound.

Similarly, vitamin A can revert the fibroblast activated state to a more quiescent phenotype. In vitro studies show that also All-Trans Retinoic Acid (ATRA), an active metabolite of vitamin A, is able to decrease matrix stiffness in cardiac and cancer fibrosis. In neonatal cardiac fibroblasts, ATRA reversed TGF-β upregulation along with cell proliferation and collagen secretion induced by Ang II treatment [149]. In the context of pancreatic cancer, treatment with ATRA, mechanically reprograms the CAF precursor pancreatic stellate cells (PSC) to promote quiescence while inhibiting pancreatic cancer cell invasion [150]. Mechanistically, ATRA reduces the ability PSC to release active TGF-β, which might otherwise act in an autocrine manner to sustain PSC activation and a tumor-favoring stiff microenvironment [151].

These observations support the notion that active metabolites of vitamin D and A might be potential candidates for the prevention and therapy of cardiac remodeling and cancer progression.

### 5.1.3. *Tranilast*

Tranilast, an analogue of a tryptophan metabolite, is identified mainly as an antiallergic drug with intriguing antifibrotic actions relevant to both cardiac disease and cancer. Administration of tranilast to cultured human cardiac fibroblasts proved successful in repressing the TGF-β/Smad signaling and dampening the Ang II stimulated fibrogenesis [152]. In addition, the drug prevented the TGF-β dependent differentiation of mesenchymal stem cells into myoFbs [153]. In vivo findings in a rat model of diabetic cardiac disease indicate that tranilast has antifibrotic actions attributable to reduced TGF-β activity [154]. Also, in a rat MI model tranilast administration started at 7 days post infarction, inhibited myocardial TGF-β1 expression, fibrosis, and left ventricle adverse remodeling [155], while a delayed treatment, started at 28 days post infarction, had no protective effects [156].

The anti-cancer activities of tranilast, either alone or in combination with chemotherapeutic drugs, have been evidenced in several preclinical studies [157]. One main mechanism of action includes targeting and modulation of TGF-β to reduce CAF function and fibrosis, as observed in experimental model of colon cancer [158] and in pancreatic CAF cell lines [159].

### 5.1.4. *Pirfenidone and Nintedanib*

Pirfenidone is an oral antifibrotic agent approved for the treatment of idiopathic pulmonary fibrosis. The drug reduces the expression of profibrotic factors such as TGF-β, and pro-inflammatory cytokines such as TNF-α, IL4, and IL-13, thus repressing inflammatory response and collagen expression. It has been reported that pirfenidone has antifibrotic activity also in various experimental settings of cardiac disease and in the clinical arena, modulating similar targets as observed in pulmonary fibrosis [160,161]. For example, in a mouse model of cardiac hypertrophy pirfenidone contrasted the profibrotic effect of Ang II in a TGF-β dependent manner [162]. Similarly, in experimental models of heart failure pirfenidone attenuated fibrosis and exhibited cardioprotective effect by repressing TGF-β/SMAD3 signaling in fibroblasts [163,164]. In two clinical studies on patients with heart failure and preserved ejection fraction pirfenidone treatment reduced myocardial fibrosis and improved the ecocardiographic parameters [165,166].

Present data suggest that pirfenidone might also exert an anti-tumor effect. In CAFs derived from patient with lung tumor, pirfenidone induced cell apoptosis and restricted TGF-β expression especially in

combination with cysplatin [167]. These findings were confirmed in non-small cell lung cancer where the drug interfered with tumor-stroma composition by inhibiting CAF activation and TGF-β production [168]. In in vivo xenograft model of triple negative breast cancer, pirfenidone prevents CAF proliferation and activation of TGF-β signaling, while synergizing with doxorubicine to slow down tumor growth and metastasis formation [169].

Nintedanib is a thyrosin kinase inhibitor approved for the management of idiopathic pulmonary fibrosis, but it has also revealed effective in cardiac disease and cancer. In a murine model of HF, nintedanib remarkably reduced cardiac fibrosis and targets the TGF/SMAD3 signaling to prevent myofibroblast transformation and production of fibrogenic proteins [170]. Also, in CAFs from patients with lung adenocarcinoma nintedanib dose-dependently inhibited the TGF-β1-induced expression of a panel of profibrotic activation markers [171].

#### 5.1.5. Natural compounds and natural compound analogues

Very recently, a library of natural compounds was screened in primary human cardiac fibroblasts (HCFs) to identify new putative candidates for the treatment of cardiac fibrosis. Among these molecules, the steroid bufalin (from Chinese toad venom) and the alkaloid lycorine (from *Amaryllidaceae* species), have been validated as effective antifibrotic agents both in in vitro and in vivo studies [172].

Successively, analogues of those natural compounds with greater effectiveness have been developed by combining in vitro validation studies, in silico prediction, and large OMICs-multi-panel-based mechanistic studies. Tested in HCF cultures and in ex vivo human myocardial slices, certain analogues were more effective than nintedanib and pirfenidone in inhibiting HCF proliferation and in promoting the expression of an antifibrotic program, even at lower concentrations. In particular the lycorine analogue lyco-s (also known as homoharringtonine) exhibited the strongest antifibrotic properties leading to a nearly complete inhibition of ECM production at concentrations 100-fold lower than lycorine without inducing cellular toxicity [173]. Trascriptomic analysis revealed that the main pathways affected by natural compound analogues were TGF-β signaling, ECM synthesis and degradation, and myoFbs regulation, which encourages testing their effects in other fibrotic disease sharing the same triggering factor, including cancer.

### 5.2. $Ca^{2+}$ signaling blockers

As a ubiquitous secondary messenger, intracellular free calcium $Ca^{2+}$ regulates a number of specialized cellular functions including secretion, metabolism, differentiation, proliferation and contraction. In particular, $Ca^{2+}$ signaling in fibroblasts plays a critical role in fibrosis-related disorders. In heart disease and cancer altered $Ca^{2+}$ handling greatly contribute to the remodeling of ECM components, leading to cardiac and tumor stiffness [28,37,174,175]. Therefore, calcium signaling antagonists have attracted attention as putative protective agents against profibrotic disease evolution.

$Ca^{2+}$ channels blockers have been shown to decrease cardiac fibrosis in different animal studies. The long-term administration of mibefradil, verapamil, and tetrandrine attenuated adverse cardiac remodeling and improved ventricular function in rats with ischemic heart failure or hypertension [176,177].

In breast cancer CAFs, pharmacological inhibition of two voltage gated calcium channels, $Ca_V1.2$ or $Ca_V3.2$ with the calcium channel blockers nimodipine or ML218, significantly impaired CAF activation [178].

Another critical regulator of calcium signaling is the intermediate conductance $Ca^{2+}$-activated potassium channel ($K_{Ca}3.1$). Through the regulation of cell membrane potential, $K_{Ca}3.1$ plays a central role in activation, migration and proliferation of fibroblasts and has been involved in the development of many pathologies with an important fibrotic component, such as cardiovascular disease, and cancer [179,180]. So far two drugs have been developed to specifically target the $K_{Ca}3.1$ channel, TRAM-34 and senicapoc. In rodent models of cardiac fibrosis induced by ventricular overload, myocardial infarction, or Ang II infusion, TRAM-34 attenuated cardiac collagen deposition and interstitial fibrosis, reduced the number of activated myoFbs, and improved cardiac function [181,183]. As demonstrated in studies on cardiac fibroblast cultures, the protective mechanisms included reduced expression of a profibrotic signature and decreased transdifferentiation of bone marrow derived cells in myoFbs [182,184]. To the best of our knowledge, the specific antifibrotic effects of TRAM-34 in tumor CAFs has never been analyzed so future studies are needed to address this crucial point.

The $K_{Ca}3.1$ selective blocker senicapoc was originally developed for sickle cell disease. Hitherto, its off-target use has been proposed in combination with chemo/radiotherapy for the treatment of therapy-resistant cancer cells [181]. Although the role of $K_{Ca}3.1$ channel in cardiac and cancer fibroblasts still awaits to be investigated, its proven safety in clinical trials raises the intriguing perspective of a rapid translation for the prevention or cure of pathological fibrosis and tissue stiffening [185,186].

### 5.3. Non-coding RNA

In addition to the above examples of drug-repositioning, novel strategies have been proposed to mitigate or reverse myoFb/CAF activation. In particular, the therapeutic potential of noncoding RNAs has been explored with success either in in vitro or in vivo animal studies [187–190]. MiRNA inhibitors or miRNA mimics are widely investigated as suppressors of profibrotic pathways and stimulators of the antifibrotic ones. Acting against the common targets of cardiac and cancer fibrosis, such molecules could represent potential treatments to apply in patients paving the way for new therapies. For example, depletion of miR-21 by use of antagomir, locked nucleic acid-modified (LNA-modified) anti-miR, or miR-sponge prevented fibroblast-to-myofibroblast transformation and proved effective in several models of cardiac fibrosis [108,191,192]. Recently an artificial circular RNA (scRNA21) has been synthetized to competitively inhibit miR-21 activity. As many naturally occurring circRNAs, this molecule acts as a sponge to achieve a specific loss of function of the target miRNA. The effectiveness of this strategy has been validated in vitro in gastric cancer cells and is predicted to also extend to other cell types in which miR-21 is highly enriched such as cardiac and cancer fibroblasts. More research is required to test the translatability of this approach as an effective antifibrotic strategy in patients with cardiac disease or cancer [189].

Another approach deals with the delivery of synthetic analogues of antifibrotic miRNAs that are present at low level in people with disorders characterized by fibrosis. For example in the last years MRG-229, a refined mimic of miR-29 has been designed to replicate the antifibrotic biological activity of its natural counterpart [193]. This molecule has demonstrated antifibrotic activity in in vitro human model systems Moreover, preclinical in vivo data in rodents and non-human primates attest its efficacy and safety at doses compatible with clinical use [193]. Although MRG-229 has been intended for pulmonary fibrosis, its molecular targets are common to other profibrotic disease, so that miR-29 replacement may represent a novel paradigm in the treatment of further pathologic conditions with a relevant fibrotic component, including cardiac disease and cancer.

These findings encourage further preclinical works to fine tune efficacious anti fibrotic therapies against cardiac and cancer stiffness based on non-coding RNA.

## 6. Conclusion and future perspectives

Cardiovascular disease and cancer are the two leading causes of death worldwide. Although often considered separate fields, cardiology and oncology are frequently intertwined. Indeed, cardiac and cancer

disease possess common risk factors, coincident in an ageing population (e.g., obesity, diabetes, smoking), and are also biologically connected through some deleterious effects of anticancer treatment on cardiovascular health [3]. Therefore, finding common druggable targets may be particularly useful, not only for the cardiology and oncology arena, but also for the increasing cardio-oncology discipline. Activated myoFbs and CAFs orchestrate cardiac and cancer fibrosis progression resulting in disease worsening. We propose that delving into myoFb/CAF similarities could be useful for the identification and implementation of innovative therapeutic options. As summarized in this review, myoFbs/CAFs share several biological properties and signaling pathways such as: TGF-β dependent cascades, metabolic reprogramming, mechanical regulation, secretory proteins, and non-coding RNAs, that could offer opportunities for novel common treatment strategies. Oligonucleotide-based strategies represent attractive options to achieve antifibrotic effects via miRNA-gain or loss of function. Though promising, this approach requests a long development time given several still unresolved challenges including efficient delivery, cell specificity, and the ability to escape recognition by the Pattern Recognition Receptors, which would otherwise induce poor tolerability. Currently, the repositioning of long used drugs can represent a faster, low risk, and economically attractive way for developing effective antifibrotic agents against cardiac and cancer disease. Contemporary technologies, including high throughput profiling and computational tools, as well as better curated database of drug repositioning clinical trials, are expected to make drug repurposing large-scale, systematic, and deliberate rather than opportunistic or serendipitous.

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## Declaration of competing interest

No conflict interest

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