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Fibroblast activation protein: Pivoting cancer/chemotherapeutic insight towards heart failure

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Abstract

An important mechanism for cancer progression is degradation of the extracellular matrix (ECM) which is accompanied by the emergence and proliferation of an activated fibroblast, termed the cancer associated fibroblast (CAF). More specifically, an enzyme pathway identified to be amplified with local cancer progression and proliferation of the CAF, is fibroblast activation protein (FAP). The development and progression of heart failure (HF) irrespective of the etiology is associated with left ventricular (LV) remodeling and changes in ECM structure and function. As with cancer, HF progression is associated with a change in LV myocardial fibroblast growth and function, and expresses a protein signature not dissimilar to the CAF. The overall goal of this review is to put forward the postulate that scientific discoveries regarding FAP in cancer as well as the development of specific chemotherapeutics could be pivoted to target the emergence of FAP in the activated fibroblast subtype and thus hold translationally relevant diagnostic and therapeutic targets in HF.

Keywords

Heart failure; Fibroblast activation; Extracellular matrix

1. Introduction

The clinical manifestations of heart failure (HF), which include dyspnea, pulmonary and peripheral edema, and exercise intolerance, carries a significant morbidity, mortality, and socioeconomic cost [1–8]. For example, the survival of HF patients requiring frequent hospitalizations due to worsening symptoms carries a 5 year mortality rate that is comparable to aggressive, malignant forms of cancer. [9,10]. However, unlike cancer, the phenotyping and staging of HF in terms of underlying structural and molecular changes

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has been a relatively new concept. [11–16] As such, an improved understanding of the specific molecular pathways involved in HF may provide for improved specificity and effectiveness of therapeutic strategies. While a fairly broad categorization, there is now a general consensus that HF can be classified into two major phenotypes: HF with a reduced ejection fraction (HFrEF) and HF with a preserved ejection fraction (HFpEF), and the prevalence of these forms of HF appear to be equivalent. [1–4,17] Underlying both of these HF phenotypes are specific changes in left ventricular (LV) myocardial structure and function collectively termed as myocardial remodeling. [18–23].

The LV myocardial remodeling process in these HF phenotypes are distinctly different. While an oversimplification, HFrEF most commonly arises from an ischemic etiology whereby HFpEF often arises from a prolonged LV pressure overload. In HFrEF, a loss of contractile units and degradation of the normal extracellular matrix (ECM) structure and composition occurs. [15,18,21] With respect to HFpEF, the underlying pathophysiology is distinctly different whereby LV ejection performance remains within normal limits, but LV filling is impaired (i.e. diastolic failure), which is due at least in part to a loss of normal LV myocardial compliance and abnormal ECM accumulation (generically termed “fibrosis”). [16,22,24,25] Thus, while the etiology and remodeling process in these HF phenotypes are different, both are accompanied by structural changes within the ECM and the emergence of an abnormal fibroblast population. [26–34] An important process in the localized spread of a primary tumor is through metastasis, whereby degradation of the normal ECM is accompanied by the emergence and proliferation of an activated fibroblast, termed the cancer associated fibroblast (CAF). [35–45] Indeed targeting specific biological pathways relevant to the CAFconstitute a chemotherapeutic target. [38,43–45] More specifically, an enzyme pathway identified to be amplified with local cancer progression and proliferation of the CAF, is fibroblast activation protein (FAP). [46–53] Accordingly, the purpose of this review are 2-fold. First, was to examine the myocardial fibroblast in normal and HF states and compare and contrast phenotype similarities to the CAF. Second, to focus upon FAP as a specific chemotherapeutic target first in the context of cancer, which would hold relevance to HF. The overall goal was to put forward the postulate that scientific discoveries of ECM remodeling in cancer as well as specific chemotherapeutics could be pivoted to target the emergence of the activated fibroblast subtype and thus hold translationally relevant diagnostic and therapeutic targets in HFrEF and HFpEF.

2. The emergence of an activated myocardial fibroblast in HF

The fibroblast is primarily of mesenchymal origin and the biological function of this cell type is context dependent. While the origins, nomenclature, and precise identification of myocardial fibroblasts remains an area of active research and a subject of debate, there is no question that a proliferation of fibroblasts, which differ from normal myocardial fibroblasts occurs with LV remodeling and HF.[26–34] The focus of this review will not be to attempt a consensus view on fibroblast nomenclature, but rather to examine the relevance of changes in fibroblast form and function as it relates to both HFrEF and HFpEF and the potential interrelationship with the CAF.

In general terms, the fibroblast is one of the most numerous cell types within the myocardium and maintains ECM homeostasis through the production of collagens, glycoproteins, proteoglycans, as well as a portfolio of degradative enzymes, which on balance, maintain normal LV architecture and geometry. [26,34,54–57] Indeed, inhibition of myocardial fibroblast maturation during cardiac development has been shown to cause a dysmorphic myocardial structure. [54] In addition to a central role in the maintenance of LV myocardial structure, myocardial fibroblasts may also regulate the transmission of mechanical and electrical signaling. [58–60]. In normal steady-state conditions, myocardial fibroblasts are relatively quiescent in terms of ECM synthesis and turnover. However, following exposure to pathophysiological stimuli, such as ischemia, inflammation, or increased mechanical load, activation of fibroblasts occurs. While an imprecise term, myocardial fibroblast activation can be defined as shifts in proliferation, resistance to apoptosis, and most importantly, alterations in form and function. [26–34,54–67] The emergence of these activated myocardial fibroblasts in terms of phenotype can occur as subpopulations, or niches, and are likely dependent upon the microenvironment and operative stimuli. As outlined in the next sections, there are distinct differences but also commonalities regarding the emergence of activated myocardial fibroblasts in HFrEF and HFpEF.

2.1. Myocardial fibroblasts in HFrEF

Ischemic injury to the myocardium, primarily due to either transient or permanent coronary artery obstruction, can result in cardiomyocyte death - i.e. myocardial infarction (MI). Interestingly, non-cardiomyocytes, in particular fibroblasts, are much more resistant to ischemic injury. [60,61] The myocardial injury such as that with MI induces a sequential series of events, which are not dissimilar to a canonical wound healing response: inflammatory, proliferative, and maturation. During each phase, the phenotype and function of the myocardial fibroblast appears to differ temporally and is dependent on both signaling and interactions with innate immune cells as well as microenvironment conditions. In the inflammatory phase, there is an emergence of a proinflammatory myocardial fibroblast phenotype, expressing various pro-inflammatory cytokines, chemokines, and ECM degrading matrix metalloproteinases (MMPs). [27,61–63] For example, reactive oxygen species and inflammatory cytokines such as interleukin (IL)-1β and tumor necrosis factor (TNF)-α can lead to the activated myocardial fibroblast phenotype. [30,60–63] The proliferative phase is accompanied by a reduction in inflammation and the emergence of potent growth factors, such as transforming growth factor-beta (TGF). [27,64,65] These signals drive the emergence and expansion of a highly proliferative population of activated fibroblasts within the MI region, which produce abundant ECM proteins but also a large portfolio of MMPs. As such, a constant cycle of ECM synthesis and degradation within the MI region occurs due to the emergence of this activated fibroblast population. During the maturation phase, there is a reduction in the density of activated myocardial fibroblasts within the MI region, but subpopulations of activated myocardial fibroblasts persist which causes continuous ECM turnover and incomplete MI scar maturation.

While the post-MI remodeling process has been placed in the context of a canonical wound healing response, there is not a period of quiescence within the MI region, unlike the scar

formation of other tissue types. Specifically, the continuous turnover of the ECM within the MI region due to the expansion and persistence of activated fibroblasts results in an unstable ECM. In turn, this leads to an MI region that is subjected to deformation due to local LV stress–strain patterns leading to a milestone event in HFrEF progression - MI expansion and LV dilation. [19–22,28–30,60–63] Thus, the emergence, proliferation, and persistence of a fibroblast phenotype that expresses not only ECM proteins but a large portfolio of degradative enzymes that can contribute to the development and progression of HFrEF.

2.2. Myocardial fibroblasts in HFpEF

The HFpEF phenotype is characterized by LV myocardial hypertrophy - that is, growth of both the cardiomyocyte and expansion of the ECM. The canonical stimulus for HFpEF is that of prolonged pressure overload due to hypertension, arterial/aortic stiffening as a function of age, aortic stenosis, or a combination of these factors. The pathophysiology of HFpEF is that of impaired LV filling during diastole, hence often termed diastolic dysfunction. The diastolic dysfunction with HFpEF is due to defects in both active relaxation processes and passive relaxation. [11,50,66,67,76] This impairment in LV passive relaxation is due to increased LV myocardial stiffness secondary to increased ECM content with HFpEF. [24–26,64,66–69] This ECM accumulation, generically termed “fibrosis,” is the result of an expansion of a proliferative fibroblast phenotype, which supplants the normal quiescent fibroblast alteration of the myocardial ECM to maintain myocardial homeostasis [31–34]. Specifically, the activated myocardial fibroblast that arises from a prolonged LV pressure overload expresses proteases, which degrade the normal ECM and in turn are replaced with a dense, thickened ECM. Ultimately, these alterations to the myocardial ECM composition and structure cause increased LV myocardial stiffness and impaired LV filling – the physiological underpinning of HFpEF.

3. Fibroblast activation protein

While the emergence and expansion of an activated fibroblast population has been a relatively recent finding with respect to HF, an activated fibroblast population has been well documented previously in both cancer as well as fibroproliferative diseases such as scleroderma. [35–53,70,71] In cancer, these activated fibroblasts have been identified as highly proliferative, apoptosis-resistant and express proteolytic enzymes within the tumor microenvironment, which in turn enhance tumor invasion, metastasis, and angiogenesis. In particular, these activated fibroblasts express a unique protease not found in quiescent fibroblasts - fibroblast activation protein (FAP). [46–53] In early studies by Rettig et al., characterization of FAP as a serine protease and relation to growth factor processing was identified and that FAP emerged in transformed cell lines. [72,73] The substrates for FAP are diverse, clearly play a role in fibroblast activation and ECM remodeling, [47–50,74–80] and as such likely contribute to both cancer and HF progression. Thus, FAP will be the focus of the subsequent sections of this review.

3.1. FAP and the cancer associated fibroblast

Although expressed at nominal levels in quiescent, normal fibroblasts, increased FAP mRNA levels as well as protein levels have been detected in CAFs in the tumor stroma

of over 90 % of epithelial cancers, such as gastrointestinal, breast, ovarian, and lung cancers (Table 1). Moreover, as shown in Table 1, there is an association between FAP levels and clinical outcomes. The mechanisms by which FAP increases tumor aggressiveness and poor prognosis in the context of cancer are multifactorial and include ECM degradation and remodeling, promoting angiogenesis, increasing cancer cell invasion and migration, enhancing lymph node metastasis, stimulating cell cycle activation, and promoting growth of CAFs. The ECM proteolysis by FAP, directly and indirectly, promotes the invasion of tumor cells, and the persistent expression of FAP within the tumor stroma, primarily localized at the invasive front, suggests this protease plays an important role in tumor metastasis. [53,82,88,89,102] A *meta*-analysis across immunohistochemistry based studies in multiple tumor types reported consistent results of increased FAP protein levels correlating with increased lymph node metastasis and decreased overall survival.[51] Furthermore, FAP positive primary tumors resulted in significantly increased lymph node metastasis compared to primary tumors that do not express FAP.[90] In gastric carcinoma, for example, increased FAP levels in CAFs is correlated to higher tumor grade, lymph node and peritoneal invasion, and decreased overall survival. [60] Another study reported an association between the level of FAP in CAFswith the degree of differentiation, depth of tumor invasion, and staging of gastric carcinoma. [52,99,100] Furthermore, invasion and migration abilities of gastric carcinoma cell lines were significantly increased when co-cultured with FAP positive CAFs.[53] Conversely, invasion and migration were significantly decreased when gastric carcinoma cell lines were co-cultured with RNA silencing mediated knockdown of FAP in CAFs. [53] The ECM degrading capacity of FAP through direct proteolysis or through activation of MMPs, allows for invasion and metastatic cancer progression. [46,48,50,75,78,91,95,97,98] What appears to be a uniform finding is that the magnitude of FAP expression, particularly in the activated fibroblast population, contributes to cancer progression. Thus, targeting FAP, particularly with respect to the CAFs, serves as a promising chemotherapeutic target, which is discussed in a subsequent section.

3.1.1. FAP and Non-Cardiac ECM remodeling—

While FAP has been a central focus in cancer, and as described in a subsequent section, changes in ECM structure in HF, FAP has also been examined in the context of non-cardiac fibrosis. For example, Levy et al identified that FAP expression was increased within regions of active fibrosis in hepatic cirrhosis.[103] With cirrhosis, FAP levels have been associated with the severity of the disease,[104] and appears to activate a subset of fibroblasts and macrophages within the liver and thereby promote fibrotic progression.[105,106] In patients and animals with renal fibrosis, increased FAP radiotracer uptake has been identified in patients with renal fibrosis. [107,108] Increased FAP activity has been implicated in the progression of osteoarthritis through direct and indirect collagen proteolysis.[109,110] Increased FAP radiotracer uptake and activity has also been identified with the inflammatory cascade in rheumatoid arthritis. [111,112].

3.2. FAP structure

FAP (also referred to as Seprase) is classified as a serine protease of the type II transmembrane glycoprotein. FAP belongs to the post-proline dipeptidyl aminopeptidase family, sharing similarities in amino acid sequence with dipeptidyl-peptidase IV(DPP4)

(Fig. 1). [46,48,50,78,93] FAP is 760 amino acids in total, starting with a 6 amino acid cytoplasmic domain. The FAP transmembrane domain spans amino acids 7–26, with the remaining 735 of its 760 amino acids in the extracellular domain. The FAP extracellular domain contains an 8-bladed β-propeller section (400 amino acids) below an αβ-hydrolase domain (262 amino acids). [90,103–106] The β-propeller domain provides a gating function by preventing the cleavage of large cytoplasmic proteins and selectively allowing substrate access to the FAP active site. The catalytic pocket is buried between these two domains and contains the catalytic triad of Ser624, Asp702, and His734. [92,113] A 3-dimensional rendering of the propeller and catalytic domains,[92] are shown in Fig. 1.Dimerization is required for FAP enzymatic activity, and FAP exists either as homodimer or heterodimer with DPP4 [80,97] The function of the FAP intracellular domain remains unclear but may play a regulatory role. FAP exists in a membrane-bound form as well as a soluble (i.e. shed) form, the latter lacking the transmembrane and cytoplasmic domain. The shedding of the extracellular FAP domain may hold diagnostic relevance as discussed in a subsequent section.

3.3. FAP enzymatic activity and substrates

FAP is the only member of the prolyl oligopeptidase family with both dipeptidyl-peptidase and endopeptidase activities, the latter having more efficient enzymatic function. [50,92,113,114] The dipeptidyl-peptidase activity of FAP removes proline dipeptides from N-terminal sequences Lys-Pro, Tyr-Pro, Arg-Pro, and Ser-Pro dipeptides. Because the dipeptidyl-peptidase activity is a commonality among the prolyl oligopeptidase family, several FAP substrates can cross over to the structurally similar, but different enzyme, DPP4. FAP endopeptidase targets substrates with a Gly-Pro, Ala-Pro, Lys-Pro, and Ser-Pro motifs, and putative substrates are presented in Table 2. It also must be recognized that some of these FAP substrates have been predicted from in to vitro studies and may not be operative in-vivo. Furthermore, it appears that the soluble form of FAP retains enzymatic activity against certain substrates, such as alpha-anti-plasmin. [4–6,15,94] Nevertheless, for the purposes of this review, FAP substrates will be categorized into substrates involving ECM remodeling, inflammatory/wound healing pathways, and bioactive signaling molecules.

3.3.1. ECM substrates—Structural proteins and enzymes contained within the ECM are important substrates for FAP. FAP interactions with fibrillar collagens have been the subject of most research, and FAP appears to be critical in the metabolism of collagen during matrix turnover and homeostasis. [75,95,98,115,122] FAP proteolysis of collagen can occur after degradation of collagen fibers by other proteases, such as MMP-1, which cleaves collagen into ¾ and ¼ intermediate-length fragments. FAP appears to act in a synergistic and/or additive fashion with other ECM proteases, such as MMP-2 and MMP-9, which also require processing of collagen into intermediate fragments.[128] However, the terminal cleavage pattern of partially digested collagen I by FAP is unique from that of MMP-2 and MMP-9.[129] Degradation of these intermediate-length fragments has been shown to facilitate phagocytosis and internalization by macrophages and fibroblasts.[130].

In tumorigenesis, FAP processing of collagen allows for CAFs to invade the tumor stroma and subsequently cause ECM remodeling which favors tumor expansion. For example, FAP

induction caused a more parallel collagen fiber orientation which enhanced directionality and velocity of pancreatic cancer cells *in-vitro*, which was abrogated by FAP inhibition. [131] In mouse primary lung fibroblasts, FAP positive fibroblasts internalized type I collagen more efficiently than FAP null-fibroblasts.[75] In FAP null mice, it was observed that these intermediate-length collagen fragments may persist longer in the ECM due to impaired collagen processing and turnover, demonstrating the biological relevance of FAP collagen metabolism *in vivo*.[75] In addition, FAP degradation of the fibrillar collagen may facilitate cell adhesion. [122] Another putative FAP substrate with relevance to ECM remodeling is Lysyl oxidase homolog-2. Lysyl oxidase homolog-2 is an enzyme which belongs to the lysyl oxidase family and functions to promote crosslinking of collagen and elastin. [76] Lysyl oxidase homolog-2 has been implicated in processes related to cancer progression and interstitial fibrosis. [133,134].

The glycoproteins fibrillin-2 and extracellular matrix protein-1 (ECM-1) have also been identified as FAP substrates.[50,76] Fibrillin-2 is an extracellular glycoprotein which provides a scaffold for the deposition of elastin precursors as well as storage and regulation of growth factors, such as transforming growth factor -β (TGF).[135–137] Initially, it was believed that expression of fibrillin-2 was restricted to developing fetal tissues but has now been recognized in wound healing processes and cancer progression. In wound healing fibrillin-2 overexpression is observed in fibroblasts and is accompanied by higher expression of latent TGF complexes. [138] In many cancers, fibrillin-2 expression is decreased and in turn it has been postulated to lead to reduced sequestration of latent TGF, enhanced TGF processing and signaling.[136,137] ECM-1 is a multifunctional glycoprotein that interacts with other structural proteins and growth factors of the ECM, and has been implicated to contribute to cancer progression.[139] Interestingly, increased expression of ECM-1 has been identified within the LV myocardium as a function of age and within the MI region. [140].

3.3.2. Inflammatory substrates—A subset of FAP substrates associated with inflammation and wound healing pathways, include interleukin-6 (IL-6), CXC-motif chemokine-5 (CXCL5), and substance P. (Table 2).

IL-6 is a pro-inflammatory, pleiotropic cytokine expressed by several cell types, including immune cells and fibroblasts, and plays a central role in the regulation of inflammation and immune response. [141] CAFsproduce significant amounts of IL-6 and further stimulated IL-6 production. [26690480] Furthermore, IL-6 enhances production of VEGF by CAFs contributing to the induction of angiogenesis.[142] It remains unclear how FAP mediated cleavage of IL-6 would ultimately alter the IL-6 signaling cascade, but one possible outcome is that FAP may interfere with a negative feedback loop between IL and 6 and the IL-6 receptor, which in turn would lead to enhanced IL-6 production [143].

CXC-motif chemokine-5 (CXCL-5) stimulates angiogenesis, immune cell recruitment, and potentially tumor growth [136]. In the tumor microenvironment, CXCL-5 is secreted by CAFs and promotes programmed cell death protein 1 (PD-L1) expression in tumor cells, which forms an immunosuppressive microenvironment promoting survival and proliferation in cancer [145]. *In vivo* studies demonstrate post-proline N-terminal cleavage of CXCL-5

enhances potency and chemokine activity up to 3-fold [146]. While remaining speculative, and perhaps counterintuitive, CXCL-5 may undergo FAP-mediated post-translational modification yielding a truncated CXCL5 isoform with enhanced activity that further cultivates a favorable tumor microenvironment.[147].

Substance P is mainly secreted by neurons and is involved in nociception and inflammation [148,149]. Though substance P is not considered a canonical inflammatory mediator, it is associated with inflammation and is thus included here as an inflammatory substrate of FAP. Substance P acts as a modulator of immune cell proliferation rates and cytokine production [150]. Substance P has been implicated to influence cardiovascular structure and function, and in turn cardiovascular disease.[151] However, a recent pharmacotherapy for HF using a dual neprilysin/angiotensin receptor inhibitor, which may potentiate substance P, may provide beneficial effects.[150] Thus, in the context of cardiovascular disease, substance P may exert multiple effects.[151] Substance P can exert a negative feedback through activation of inhibitory NK-1 autoreceptors [153]. While remaining speculative, the proteolytic processing of substance P by FAP,[74] may interfere with this negative feedback loop and actually potentiate substance P production.

3.3.3. Bioactive molecule substrates—Another subset of FAP substrates are bioactive molecules, including B-type natriuretic peptide (BNP), Fibroblast Growth Factor-21 (FGF-21), and TGF. TGF will be the focus of a subsequent section. BNP is produced and secreted mainly by LV myocytes [154,155]. BNP production is enhanced by LV wall stress and general mechanical strain in cardiomyocytes. BNP binds to guanylyl cyclase-coupled natriuretic peptide receptors expressed by a variety of tissues and activates guanylyl cyclase A leading to an increase in the intracellular concentration of cGMP [154,155]. In addition to this BNP signaling pathway leading to natriuresis, reduced vascular tone and anti-inflammatory effects, an anti-fibrotic effect may also be operative.[156] which in turn can have salutary effects with respect to volume regulation, vascular tone and anti-inflammatory effects. BNP may also have a direct inhibitory effect on cardiac fibroblast function through extracellular signal-related kinase activity and reduced expression of a number of “profibrotic” genes. [157] A past study identified that FAP inhibition enhanced the cardioprotective effects of BNP in the context of myocardial ischemia.[117] Moreover, BNP, and the pro-form of BNP, (NTpro-BNP) are well-recognized biomarker associated with both HFrEF and HFpEF. [158,159] Thus, the fact that BNP is a substrate for FAP would hold both biological and clinical significance in the context of HF. First, FAP mediated degradation of BNP would contribute to profibrotic and proinflammatory states. Second, accelerated BNP degradation by FAP would potentially confound diagnostic and therapeutic utility.

FGF21 transduces endocrine signaling through Klotho protein co-receptors and fibroblast growth factor receptors (FGFRs), a family of receptor tyrosine kinases involved in the regulation of cell proliferation, differentiation and survival [168]. In breast, lung, and gastric cancer FGFRs are upregulated and likely contribute to cancer progression. [168]. Interestingly, Dunshee et al identified that FGF-21 is a substrate for FAP, whereby FAP mediated proteolysis of FGF-21 will impair FGR signaling.[160] Whether and to what

degree FAP may influence FGF-21 signaling HF remains unclear, but it is notable that increased FGF-21 has been identified in HF. [161,162].

3.4. FAP and the influence of fibroblast proliferation and phenotype

FAP can modify the ECM through both proteolytic substrate processing as well as influencing fibroblast form and function. For example, and discussed further in the chemotherapeutic section, pharmacological inhibition of FAP decreased an index of CAF density within the tumor stroma.[163] It has been demonstrated that in fibroblast cultures from human uterine fibroids, an RNA interference strategy which partially silenced FAP expression concomitantly reduced ECM components such as collagen type 1, fibronectin and laminin measured by immunoblotting[164] In fibroblast cultures taken from colorectal carcinoma, directional shifts in secretome profiles occurred when a gain of function and loss of function strategies for FAP were employed.[50] Specifically, using a proteomics approach, a gain of FAP resulted in increased levels of TGF and ECM components such as collagen type I and lumican. Using a collagen gel contraction assay, this past study identified that collagen degradation rates directionally changed in proportion to FAP activity. Finally, it was demonstrated that a loss of FAP activity resulted in a shift in fibroblast phenotype defined as a reduced spindle-shaped morphology and smooth muscle-actin expression. Additional studies employing secretome profiling in CAFs, demonstrated that increased FAP levels were associated with increased MMP expression, specifically MMP-1 and MMP-9. [50,165] Taken together FAP can directly alter fibroblast phenotype as well as proteolytic profiles. The fact that FAP can cause MMP expression in CAFswould suggest a feed forward mechanism by which FAP could amplify local ECM proteolytic pathways.

3.5. FAP regulation

In this section we detail the transcriptional, post-transcriptional, and post-translational regulation of FAP. However, this section is not meant to be comprehensive as FAP regulation remains an area of active research.[166–168] In terms of endogenous inhibitors of FAP, Wei et al reported that osetolectin can inhibit FAP. [169] However, there appears to be no upregulation of endogenous inhibitors of FAP with increased FAP activity, and as such regulation of FAP at the transcriptional, post-transcriptional, and post-translational level constitute the critical checkpoints.

3.5.1. Transcriptional regulation—A number of bioactive signaling molecules have been identified to contribute to the expression of FAP. For example, in a study utilizing immunofluorescence analysis of a mouse embryonic fibroblast cell line demonstrated that TGF robustly increased FAP mRNA levels, and an additive effect was observed with coincubation with IL-1β. [170] Rettig et al identified that TGF increased FAP expression in stromal fibroblast cultures. [72] In human bone marrow mesenchymal stem cells, incubation with TGF or IL-1β increased FAP mRNA levels by approximately 2-fold. [170] FAP promoter analysis have identified downstream signaling of TGF through EGR-1[171] and SMAD3[172] binding sites. Notably, FAP expression is increased in adult human myocardial fibroblasts through the SMAD2/SMAD3 pathway [173].

Less is known about the negative regulation of FAP. FAP expression has been observed to have minimal to undetectable expression in mouse fibroblasts cultured on 2D silicon surfaces.[175,176 However, when these fibroblast were cultured on 3D silicon nanowire arrays, FAP upregulation was observed within the fibroblast filopodia, and this expression was inversely proportional to the length of the nanowires, indicating biophysical stimuli can regulate FAP expression to some degree. [174] In a study utilizing breast cancer fibroblast constructs, it was observed that the tumor suppressor phosphatase and tensin homolog deleted from chromosome ten(PTEN), was a negative regulator of FAP. [176].

3.5.2. Post-transcriptional regulation—One probable mechanism for FAP post-transcriptional control is through microRNAs (miRs). The miRs regulate mRNAs by degradation, translational inhibition, or translational activation. A summary of miRs which have been identified in the potential regulation of FAP is presented in Table 3. Post-transcriptional regulation of FAP by miRs is likely an important checkpoint, whereas FAP mRNA levels do not result in proportional FAP protein levels.[222] As an example, using oral squamous cell carcinoma cell lines, it was determined that miR-30a-5p directly targeted FAP mRNA, which resulted in the suppression of cell proliferation, migration, and invasion. [223] It has been reported that miR-21 was a negative regulator of PTEN, and thus an FAP inducer. [224] Interestingly, miR-21 has been identified as a mediator of fibroblast activation in a multitude of pathological states including cancer and HF. [225–227] As shown in Table 3, we performed an *in silico* analysis using a sequence matching algorithm [220,221,223,224] and identified 24, 54, and 127 miRs with a 90 %,80 %,70 % miR target gene score respectively, which predicts miR interaction with FAP mRNA. Those with the highest stringency with respect to FAP gene scoring are shown provided in Table 3. In addition, we cross referenced these miRs in cancer and HF (Table 3).[228,229] This analysis revealed a number of miRs with high probability mapping to FAP were also altered in both cancer and HF. For example, a family of miRs, miR-30a-5p, miR30b-5p, and miR30e-5p mapped to FAP with high probability (>97 %) and have been identified to be altered in both cancer and myocardial remodeling/HF. For example, miR-30a-5p has been reported to hold prognostic value in terms of cancer and HF progression.[186,187] What is unclear is how a specific miR, whether it be increased or decreased, can specifically modulate FAP protein levels. Moreover, it is unlikely that a single miR is critical to FAP post-transcriptional regulation, rather a specific “cluster” of miRs may be pivotal in the regulation of FAP protein levels. One future research direction would be to examine the role of the cassette of miRs identified to map to FAP with high probability and have also been found to be altered in cancer or HF.

3.5.3. Post-translational regulation—An important post-translational interaction has been shown to exist between FAP and the TGF signaling pathway. [50,102,126,170,230] Specifically, TGF remains sequestered within the ECM through interactions with a latency activation protein (LAP) and a latency binding protein (LTBP).[231,232] The proteolytic degradation of LAP/LTBP is a key checkpoint, in which sequestered TGF is liberated from the latent complex, and allows for receptor binding. Using computational degradomics, this latency complex, notably LTBP was a high probability substrate for FAP. [76] In an *in vitro* study, when recombinant murine FAP was incubated with recombinant human LAP, LAP

underwent proteolytic degradation which could be attenuated with an FAP inhibitor. [75] In another study, using fluorescent proteolytic substrates, FAP has been shown to cleave a critical sequence of LTBP, and thus disrupt this TGF latency complex. [233] Since TGF can stimulate FAP expression, there exists a potential for a TGF/FAP amplification loop whereby FAP induces release of TGF, which then binds to TGF receptor complexes, and thereby increases FAP transcription (Fig. 2). While this remains speculative, this interaction between FAP and TGF is likely to hold implications for ECM remodeling in both HFrEF and HFpEF as discussed in a subsequent section.

As with other serine proteases, the binding/activation of FAP can result in shedding of the extracellular domain. In different tumor types, it has been observed that levels of circulating FAP were inversely proportional to levels of tumor-associated expression of FAP protein. [234,235] The exact mechanism(s) and mediators of this shedding or retention process remain unclear, but it is possible that FAP is a target of protease-mediated ectodomain shedding, which is common to other transmembrane proteins. [236] Another possible level of post-translational regulation of FAP is dimerization and glycosylation. As stated before, FAP must dimerize in order to have normal catalytic function. A conserved region within the transmembrane domain has been identified as crucial for FAP dimerization but also proper membrane trafficking, for a mutation of this region leads to intracellular accumulation of FAP.[237] It has been demonstrated that unglycosylated FAP does not retain its enzymatic function, suggesting glycosylation is required for proper folding or membrane trafficking. [113].

4. FAP in HF

4.1. FAP in HFrEF

While FAP expression is extremely low in normal myocardium, induction of FAP occurs in one of the more common causes of HFrEF- MI. [55,117,173,238,239] In patients with acute coronary syndrome, serial blood collection has identified increased soluble FAP levels, likely due to increased FAP expression and activation. [55,117] The increased plasma FAP levels were reported in the early post-MI period and were associated with adverse LV remodeling.[55] Using myocardial biopsies, increased FAP within myocardial fibroblasts in patients post-MI.[117] Postmortem studies of explanted hearts secondary to ischemic cardiomyopathy, elevated FAP protein expression by immunohistochemistry has been reported [239]. Interestingly, this study reported increased FAP throughout the LV including the MI, border and remote regions. In animal models of MI, FAP gene and protein expression is upregulated in a localized, time-dependent manner.[173,238,239] For example, FAP mRNA as well as protein levels were observed within the MI and borderzone in rats post-MI.[173] Specifically, increased FAP expression peaked at 7 days post-MI within the borderzone and slowly declined through 28 days post-MI, whereas FAP expression peaked 7 days post-MI and persisted through 28 days post MI. In a pig model of MI, FAP expression detected in the MI as well as the border and remote regions, such as the non-infarcted interventricular septum. [239] In an initial report,[238] genetic deletion of FAP in mice reduced LV remodeling in the early post-MI period. Overall, these initial clinical and animal studies identified a robust increase in FAP levels in the early post-MI period

and the emergence of a fibroblast phenotype similar to the cancer-associated fibroblast, [31–35,46–54] These studies also identified a relation to the degree of post-MI LV dilation- the harbinger for the development of HFrEF. As a result, these observations likely propelled the development of FAP imaging approaches for HFrEF as discussed in a subsequent section.

4.2. FAP in HFpEF

Unlike HFrEF, studies of FAP in the HFpEF phenotype are limited. In a rat obesity model which recapitulated some of the features of HFpEF, increased levels of FAP were identified and correlated with the degree of myocardial fibrosis.[240] However, FAP induction in obesity mouse models with features of HFpEF, has not been a uniform finding.[26] Thus, identifying the potential role of FAP in the development of HFpEF remains to be full established and research in this area has been hindered by several factors. First, in clinical studies, presentation of HFpEF is commonly at the time of symptom presentation and thus the natural history of this process and the potential early role of FAP has not been studied. A second consideration is that animal models which recapitulate the HFpEF phenotype are not as well established. One unifying observation in animal models however, is that enhanced TGF signaling is a cornerstone for the development of LV hypertrophy and ECM accumulation, critical features of HFpEF.[22–29] As discussed in a previous section, there are several intersection points for FAP activity and TGF signaling. Thus, whether and to what degree FAP expression contributes to early shifts in fibroblast function and ECM structure with the development of HFpEF is an important future research direction. Indeed, using radionuclide imaging methods, increased fibroblast activation and FAP induction has been recently reported in patients with HFpEF.[240] Since HFpEF continues to become a major contributor to the overall HF burden,[1–3,7,13,66] identifying proteolytic pathways which contribute to this process, such as FAP induction would be warranted.

5. Chemotherapeutic targeting FAP

As would be expected, chemotherapeutics have been developed which target FAP. These approaches fall into the small molecule inhibitor domain, immunotherapies, and more global DPP4 inhibitors.

Talabostat (Val-boro-pro, PT-100) is a small molecule amino boronic dipeptide that competitively inhibits dipeptidyl peptidases, including FAP and DPP4 [241–243]. Amino boronic dipeptides have a high affinity for the catalytic site of FAP due to the formation of a complex between Ser^{624} of FAP and boron of talabostat [241]. In addition to inhibiting dipeptidyl peptidases, animal models demonstrated various immune effects through increased cytokine and chemokine production in lymphoid organs and tumor mass that enhanced tumor-specific T-cell immunity and T-cell independent stimulation of antitumor activity of neutrophils, macrophages, and natural killer cells through high affinity interactions involving FAP [242,243]. Pre-clinical studies of talabostat indicate inhibition of FAP proteolytic activity with a high affinity and clinically applicable pharmacokinetics.[244,245] Representative clinical studies of talabostat are summarized in Table 4. Overall, these studies were performed in patients with advanced stage cancer and often in combination with other chemotherapeutics, with equivocal or negative outcomes.

One important outcome from these studies was the identification that talabostat had effects on immune pathways, such as cytokines and chemokines.[241,242,248] As indicated in a previous section, likely substrates for FAP include specific cytokines and chemokines and thus FAP inhibition by talabostat likely potentiated these inflammatory pathways as well as the innate immune response such as the inflammasome.[242,256] Thus, systemic delivery of talabostat likely produced multiple downstream effects due to FAP inhibition which could result in problematic issues with respect to clinical efficacy and outcomes. For example, talabostat treatment in combination with other chemotherapeutics in patients with metastatic melanoma was associated with peripheral edema in approximately 10 % of patients. [251] Another small molecule with much higher specificity for FAP is the radiopharmaceutical identified as UAMC-1110.[257,258] This FAP inhibitor is computed to have a nearly 1000 fold higher specificity for FAP compared to other DPP4 proteases,[258] and has shown antitumor activity in mouse models of pancreatic cancer.[258] As FAP is involved in tumor invasion, metastasis, and angiogenesis, further research of early FAP inhibition prior to metastatic spread of cancer and newer generation small molecule inhibitors may yield more significant anti-tumor effects.

A variety of monoclonal antibodies (mAbs) have been developed and tested in clinical trials for FAP inhibition.[259] These mAb constructs such as the mouse mAb F19 can identify and bind to cells that express FAP and have undergone initial clinical trials.[260,261] For example, Phase I clinical trials have tested whether mAb F19 (mouse and humanized) can accurately target cells with FAP and appeared to be well tolerated [262]. Another approach has been to combine chemotherapeutics with recombinant anti-FAP strategies [264–266]. As an example, the recombinant fusion anti-FAP protein, RO6874281 has been utilized in preclinical models with programmed cell death protein-1 (PD1) checkpoint inhibition.[253] Another preclinical study tested whether the antibody-drug conjugate OMTX705 was able to successfully identify and suppress FAP-positive CAF [263]. In this report, cell viability assays containing primary cancer-associated fibroblasts identified OMTX705 to provide FAP-specific cytotoxic effects. Immunotoxins is another approach under investigation as these hold potential for selectively targeting certain cell types.[265] Since FAP contains a cell surface extracellular domain, then immunotoxins for FAP may be feasible [267,268]. One such immunotoxin, αFAP-PE38 has been reported to successfully inhibit tumor growth in a mouse breast cancer model [266]. Using a protoxin approach, liposomes containing promelittin and FAP linked substrate yielded growth inhibition in mouse model xenografts of breast and prostate cancer.[266] The developed protoxin was also much less toxic to FAP-negative cells than unmodified melittin.[269] Another immune related approach is through the use of redirected T cells with FAP-cell lysing capacity, also known as adoptively transferred FAP-specific re-directed T cells. For this approach, extracted cells undergo viral transduction producing a chimeric antigen receptor that recognizes FAP.[270–273] This has been utilized in animal models of pleural mesothelioma and has undergone initial clinical evaluation for this disease. [273,274]. In another study, chimeric antigen receptor T-cells can be directed to selectively kill FAP-expressing cells and showed effects in a number of murine mouse tumor models.[262] However, all of these immune based approaches hold a number of challenges in terms of therapeutic dosing and systemic toxicity. The development of higher affinity FAP ligands with tumor targeting specificity have been recently described,

which may overcome some of these obstacles.[275] Thus, these immune based approaches provide a proof of concept that targeting the FAP expressing fibroblast holds therapeutic potential with more selective and localized targeting approaches.

There are multiple dipeptidase IV (DDPIV) inhibitors that have been successfully advanced to clinical utility, primarily for diabetes. [276–283] Organoboronic based molecules, which includes talabostat have received attention for FAP inhibition, such as that designated as PT630.[162,164,280,281] PT630 injections in mice tumor model reduced tumor growth and was associated with reduced FAP activity. [162]. However, PT630 failed to decrease tumor growth in an immunodeficient mouse model with implanted breast cancer cells and cyclizes at physiological pH, thus reducing FAP inhibition potency. [283]. Linagliptin (trade name Tradjenta), effectively inhibits DPP4, and a much lower potency for FAP, has been investigated in patients with cardiovascular disease.[281,282] Specifically, the CARMELINA trial enrolled over 6,000 patients with type II diabetes and at increased risk for cardiovascular events.[282] This study identified that this DPP4 inhibitor did not affect the risk for the development or progression of HF, which hold promise for the potential safety for more selective FAP inhibitors. However, it remains unclear whether DPP4 at doses used in these past clinical trials significantly affects FAP levels and/or activity, or the potential cardiovascular benefit are due to secondary effects on metabolism/inflammation. [284,285] As discussed in the next section, newer modalities of measuring FAP activation may provide insight into this issue.

6. Future directions

This review attempted to provide an overview of FAP in terms of fibroblast activation, ECM remodeling and how it may play a contributory role for the development of HF. The next steps in FAP research could be considered in 3 domains; investigations into the biology of FAP and profiling, FAP imaging and finally FAP therapeutics.

6.1. FAP biology and profiling

Since FAP is expressed at relatively low levels in the LV myocardium, it remains unclear what role FAP may play in maintaining normal ECM structure and signaling pathways. While FAP induction has been identified in both HFrEF and HFpEF, the temporal pattern of FAP expression and the specific substrates/pathways may be distinctly different and warrant future study. For example, in HFrEF which can develop from a MI, ECM degradation and instability occurs within the MI region whereby FAP may degrade ECM components directly or indirectly by MMP activation. In HFpEF, FAP expression in myocardial fibroblasts can induce TGF activation and contribute to myocardial fibrosis- a key structural event with HFpEF In terms of FAP regulation, identification of whether an endogenous inhibitor of FAP occurs in HF would likely yield important insight into FAP regulation. As stated previously, a specific set of miRs map to FAP and how shifts in these miRs would affect FAP expression and thus LV remodeling in both HFrEF and HFpEF remain to be examined. The portfolio of FAP known and potential substrates was put forward in this review, but is unlikely complete. Moreover, the increased expression of FAP may alter existing biomarkers used for HF diagnosis and prognosis, such as NTpro-BNP and what

confounding effects this may have warrant study. Finally, this review has identified many common characteristics between the CAF and the fibroblast population which emerges with HFrEF and HFpEF. What remains unclear is whether this fibroblast phenotype emerges from existing LV myocardial fibroblasts or from a circulating cell type which undergoes expansion within the myocardium, or a combination of these sources.

Since the extracellular domain of FAP is “shed” during activation and interaction with proteolytic substrates, then presumably this would be a potential biomarker for FAP activation which can be detected from peripheral blood sampling. Indeed, as detailed previously, proof of concept clinical studies have reported that soluble FAP can be detected using immunoassay approaches.[55,117] This approach would allow for a non-invasive method to serially measure FAP over time and thus allow serial measurements during the development and progression of HFrEF or HFpEF. However, as with any blood based biomarker, how labile soluble FAP may be in the systemic circulation and the source of the soluble FAP can be confounding factors. Uitte et al identified that plasma FAP levels using both an activity assay and an immunoassay were elevated in patients with hepatic dysfunction and fell following liver transplantation.[104] Moreover, this past study identified the impact of different blood sampling conditions in terms of quantifying soluble FAP levels.

6.2. FAP imaging

Since increased FAP expression and activation has been implicated in cancer and metastasis, then a logical direction would be the development of FAP imaging modalities. Indeed, a positron emission tomography (PET) approach has been advanced which utilizes ^{68}Ga-labeled, ^{18}F-labeled or ^{64}Cu-labeled FAP inhibitors.[55,81,286–294] This class of FAP targeted radiolabeled PET imaging probes has been extensively evaluated in preclinical models, while several have advanced to human imaging demonstrating favorable pharmacokinetics, dosimetry, and imaging characteristics. There are also ^{99m}Tc-labeled FAPI derivatives (^{99m}Tc-FAPI-34) that could be used for SPECT imaging of FAP in the heart.[285].

In this review we will focus on the use of ^{68}Ga-FAPI derivatives for PET imaging, since this class of PET imaging agents has the largest body of data related to cardiac imaging. In a rat MI model, ^{68}Ga-FAPI PET imaging was performed and identified peak uptake at 6 days post-MI. [81] Using autoradiography and histological staining, the predominant ^{68}Ga-FAPI binding was observed along the MI border zone. In an isoproterenol induced HF rat model, ^{68}Ga-FAPI uptake peaked at 7 days post isoproterenol injection and was associated with the development of myocardial fibrosis.[286] In LV pressure overload induced hypertrophy in rats, ^{68}Ga-FAPI uptake was identified at 2, 4 and 8 weeks with a peak level identified at 4 weeks post pressure overload.[287] Moreover, the peak ^{68}Ga-FAPI uptake at 4 weeks post LV pressure overload was associated with the onset of definable histological evidence of myocardial fibrosis. Taken together, these animal studies suggest that PET based ^{68}Ga-FAPI imaging holds potential to identify LV myocardial FAP induction in both HFrEF and HFpEF.

In clinical studies, PET based ^{68}Ga-FAPI imaging has been predominantly focused upon cancer, but incidental findings of FAP activity within the LV myocardium was reported

in patients with cardiovascular risk factors.[289,290] For example, in a cohort of 229 patients with cancer metastasis, focal ^{68}Ga-FAPI enhancement was observed in patients with established cardiovascular risk factors.[290] In an initial imaging study in patients following an MI (within 11 days), ^{68}Ga-FAPI uptake was identified and extended beyond the perfusion defect, and the magnitude of the FAP radiotracer uptake was associated with subsequent adverse LV remodeling.[55] In a small cohort of MI patients with ST segment elevation, ^{68}Ga-FAPI uptake was identified to extend beyond the area of acute myocardial injury.[291] An example of PET/CT based ^{68}Ga-FAPI imaging in a patient post-MI is presented in Fig. 3.[55] There remains a number of outstanding issues with respect to FAP imaging in either HFrEF or HFpEF which include sensitivity of this approach in terms of the extent to which FAP localization and distribution can be identified beyond areas of acute myocardial injury. It is also not clear what may be the optimal FAP imaging agent, and newer and potentially more specific ^{68}Ga-based FAP ligands have been proposed.[292]. There are other pitfalls to this approach which includes non-specific binding to scar/degenerative tissue which may or may not be due to FAP activation.[293,294] There are also technical issues related to the absolute quantification of myocardial uptake these PET radiotracers based on partial volume effects associated with wall thinning. This technical issue may be overcome by use of hybrid PET/MR or contrast CT imaging to define the endocardial and epicardial edges of the myocardium. The use of hybrid PET/MR would also allow for the evaluation of changes in regional mechanics associated with regional changes in fibroblast activation. This type of integrated analysis may improve our understanding of the physiological impact of fibroblast activation in a host of cardiac disease states.

6.3. FAP therapeutics

A schematic of FAP potential therapeutics for targeting the cardiac fibroblast is shown in Fig. 4. One of the critical issues regarding FAP inhibition using either small molecules or immunotherapy/immunotoxins in the context of developing HFrEF or HFpEF is timing. The standard approach in chemotherapy is for a focused, short term pulse delivery rather than a sustained, chronic treatment. Thus, an over-arching issue will be to identify the temporal window in which targeting the emerging and proliferating FAP positive fibroblast in both HFrEF and HFpEF will be essential. As presented in the previous section, plasma profiling of soluble FAP and/or FAP imaging will be important tools to address this issue. In addition, it is likely that targeting FAP in the myocardium will require FAP imaging as a means to assess the effects on FAP activation- i.e. a theragnostic approach. With respect to small molecule therapeutics, the greatest clinical exposure is with talabostat and while this FAP inhibitor appears to be well tolerated, the effects on tumor progression have been equivocal. Whether and to what degree talabostat may be effective in animal models of HFrEF or HFpEF is an area for future exploration. As briefly presented in a previous section, the development of chimeric/hybrid antibody approaches may also be an important direction for FAP inhibition/targeting. While these will likely be initially assessed in the context of cancer and chemotherapeutics, the potential utility of pivoting these FAP chemotherapeutics towards LV remodeling and the development of HFrEF or HFpEF may hold promise. Finally, the therapeutic target for both HFrEF and HFpEF is the FAP positive myocardial fibroblast population whereas systemic delivery of FAP therapeutics, particularly for a prolonged interval will likely encounter adverse systemic effects. Thus, developing

localized delivery strategies to the myocardium which will allow for more specificity in FAP targeting would be an important direction. [295,296].

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Abbreviations:

BNP	B-type natriuretic peptide
CAF	Cancer associated fibroblast
CXCL5	CXC-motif chemokine 5
DPP4	Dipeptidyl peptidase 4
ECM	Extracellular matrix
FAP	Fibroblast activation protein
FGFR	Fibroblast growth factor receptor
FGF-21	Fibroblast growth factor-21
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
IL-1β	Interleukin-1 beta
IL-6	Interleukin-6
LAP	Latency activation protein
LTBP	Latency binding protein
LV	Left ventricle
mAbs	Monoclonal antibodies
MI	Myocardial Infarction
miR	microRNA
MMP	Matrix metalloproteinase
NTpro-BNP	N-terminal pro-B-type natriuretic peptide
PD-1	Programmed cell death protein-1

PTEN	Phosphatase and tensin homolog deleted from chromosome 10
TGF	Transforming growth factor
TNF	Tumor necrosis factor
VEGF	Vascular endothelial growth factor

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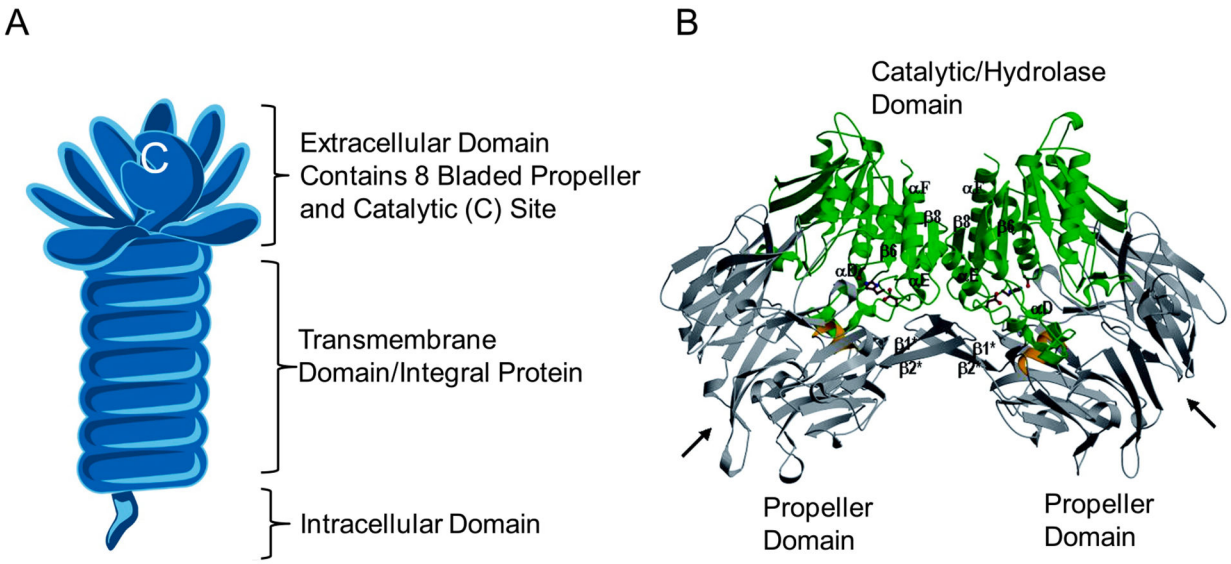

Fig. 1.

(A) A stylized schematic of FAP based upon structure–function studies[46,48,50,80,92,96,113–205]. The extracellular domain containing the 8 bladed propeller imparts substrate specificity whereby the catalytic domain (C) is an amino-acid peptidase which cleaves after a proline residue and is also an endopeptidase which cleaves a glycine-proline sequence. Thus FAP can process ECM proteins directly and also indirectly through activation/deactivation of other proteases and signaling molecules. The function of the intracellular domain remains unclear but may be a target of phosphorylation and thus play a regulatory role. (B) Ribbon diagram for the extracellular domain of FAP which identifies the propeller domains (4 on each side) in grey shading and the catalytic domain in green shading. The arrows indicate the direction where the folded propellers will form a central pore for substrate docking. Reproduced from Aertgeerts, K., Levin, I., Shi, L., Snell, G. P., Jennings, A., Prasad, G. S., Zhang, Y., Kraus, M. L., Salakian, S., Sridhar, V., Wijnands, R., & Tennant, M. G. (2005). Structural and kinetic analysis of the substrate specificity of human fibroblast activation protein alpha. The Journal of biological chemistry, 280(20), 19441–19444.

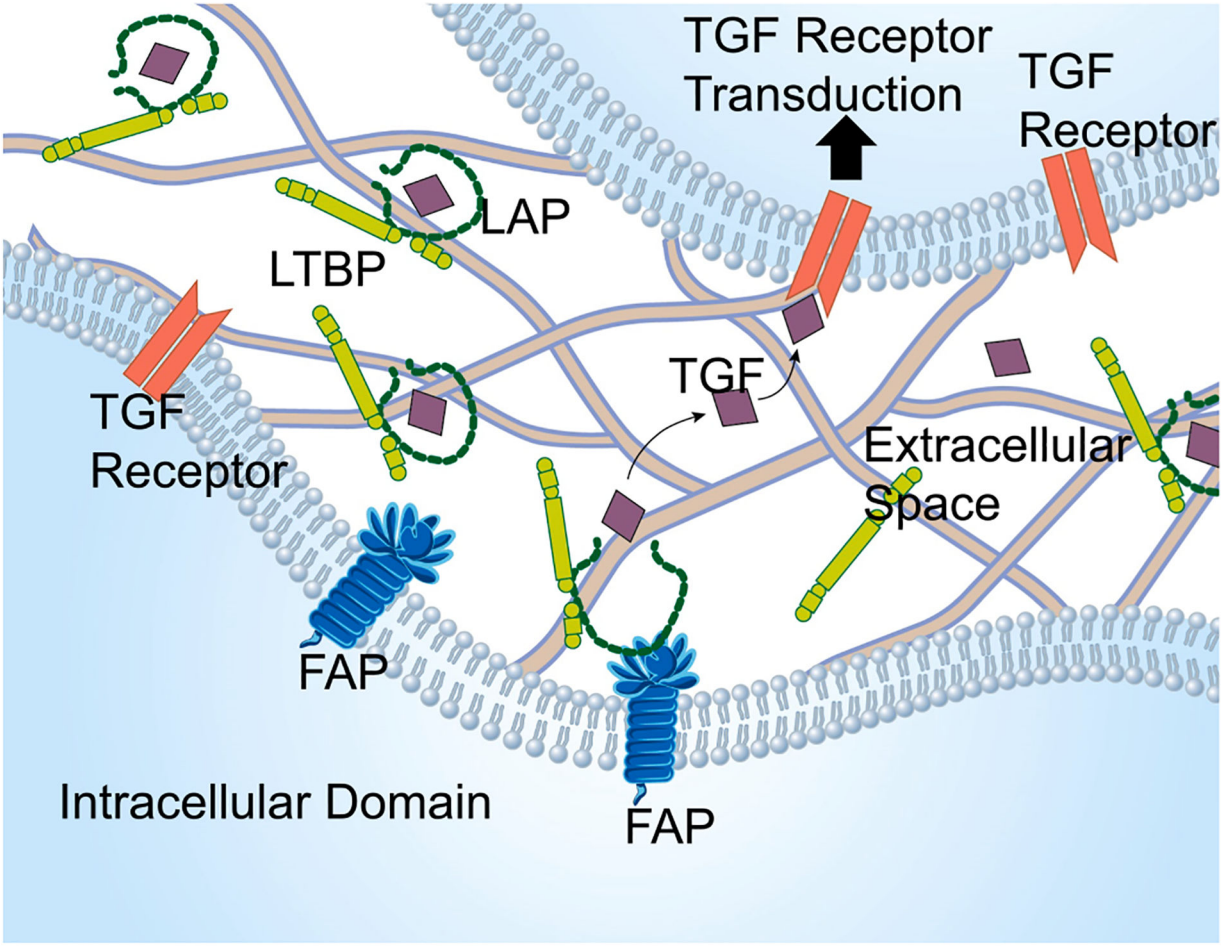

Fig. 2.

Simplified schematic for a potential FAP/TGF amplification loop. TGF is prevented from binding to TGF receptor complexes (denoted as TGF receptor) through sequestration of the latency activation protein (LAP) and latency binding proteins (designated at LTBP). In silico mapping and initial in-vitro studies,[75,76] have identified that FAP can proteolytically disrupt the LAP/LTBP complex which would result in enhanced liberation of TGF. As a consequence, TGF will bind to the TGF-receptor complex and intracellular transduction such as activation of SMADs, such as canonical SMAD3, which has been shown to cause increased FAP transcription.[172] While this is a simplified postulate of a complex proteolytic/signaling interaction, this does put forward an important post-translational event in terms of FAP/TGF and fibroblast activation and ECM remodeling.

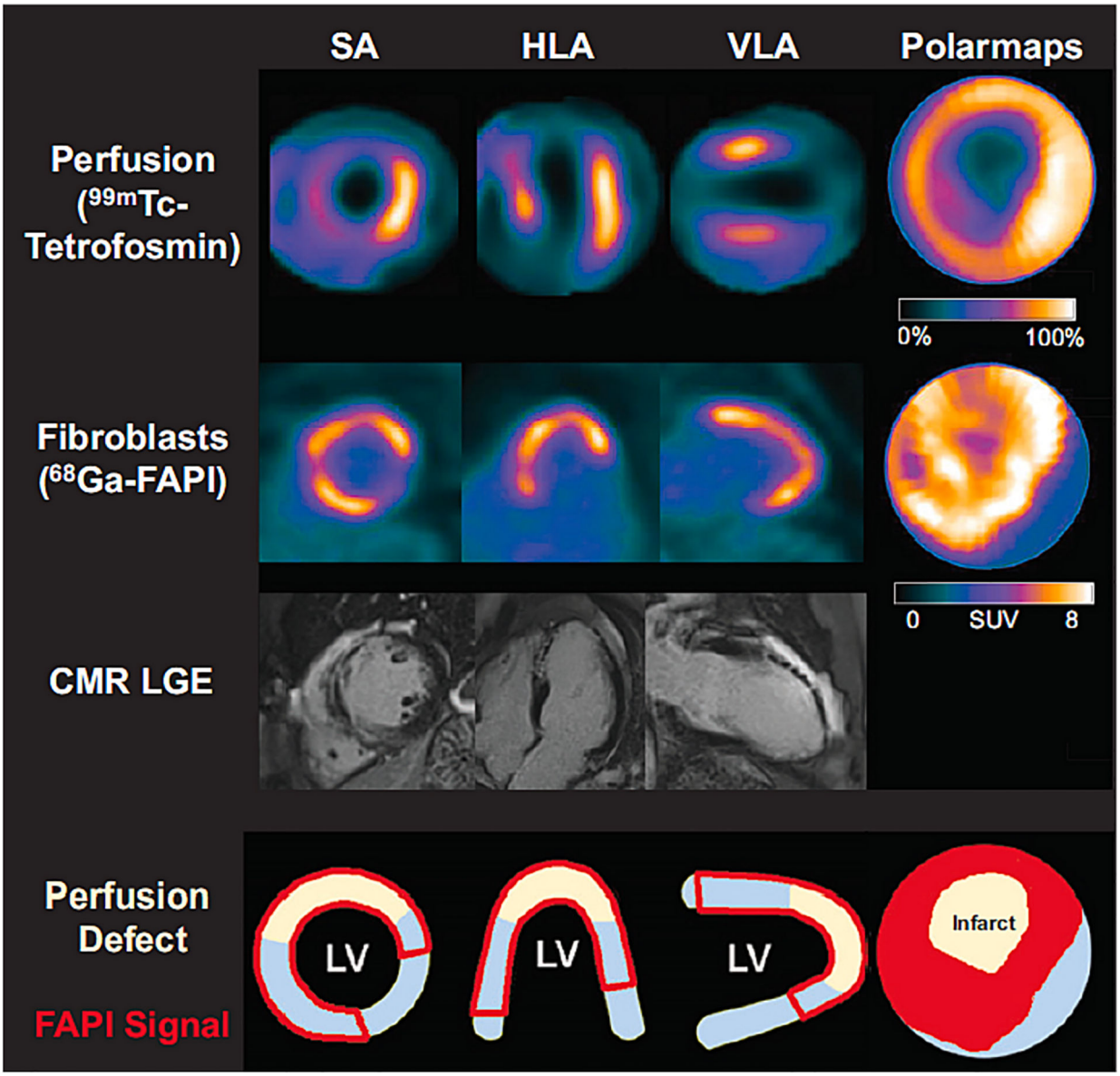

Fig. 3.

Myocardial perfusion images using ^{99m}Tc-tetrofosmin at rest, fibroblast activation by ^{68}Ga-FAPI PET, scar defined by late gadolinium enhancement (LGE) from cardiac magnetic resonance (CMR), and schematic drawings of LV. Area of fibroblast activation (red) as indicated by ^{68}Ga-FAPI-46 PET signal exceeds infarct area (yellow) and distribution of LGE signal within the ante-roseptal wall. HLA = horizontal long axis; SA = short axis; VLA = vertical long axis. This research was originally published in Journal of Nuclear Medicine. Reproduced with permission from Reference [55].

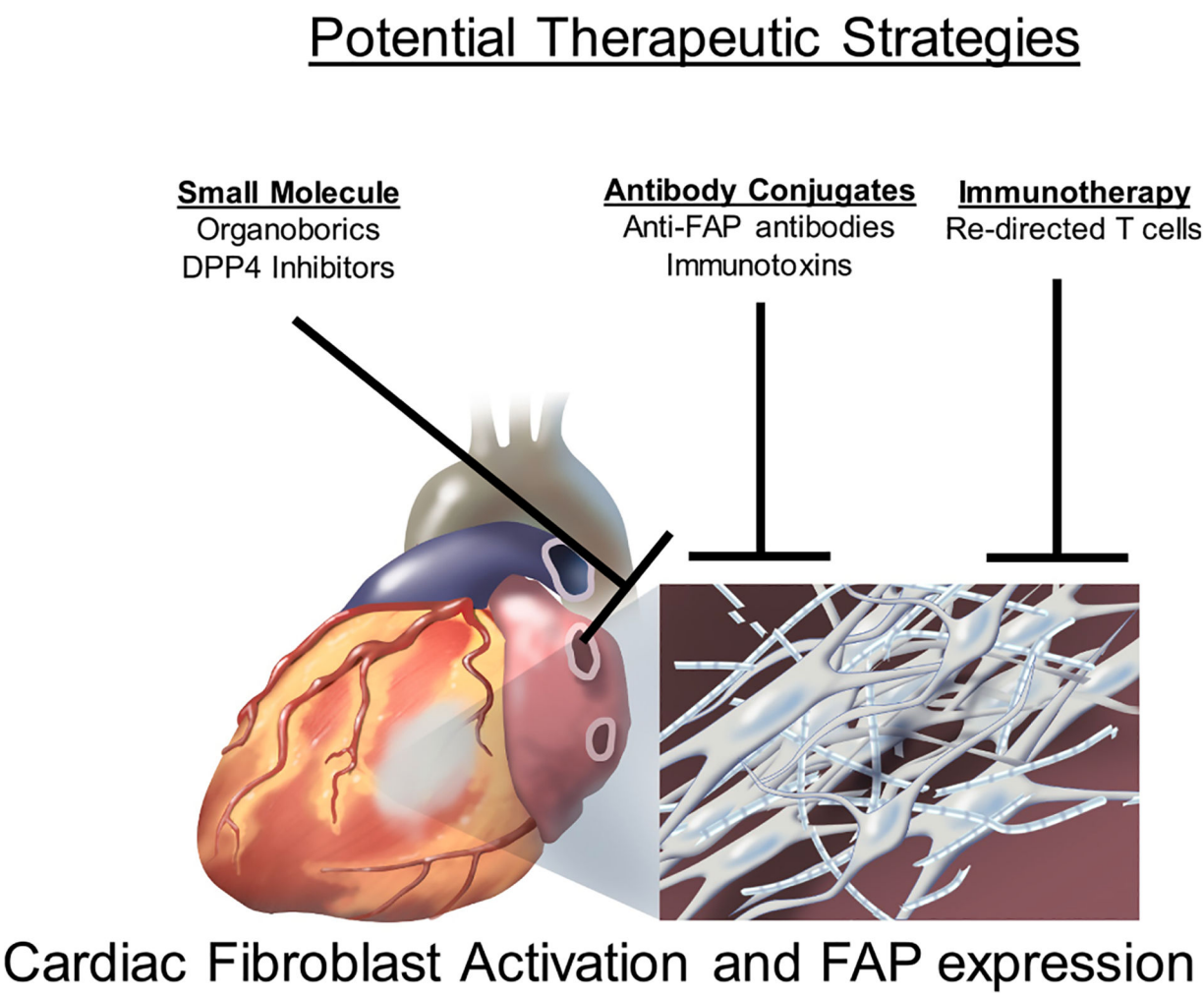

Fig. 4.

Schematic of cardiac fibroblasts proliferating and expressing FAP. These cardiac fibroblasts which emerge with LV remodeling are similar in phenotype to CAFs. Thus, potential therapeutic strategies developed for CAFs could be considered for these cardiac fibroblasts. There are 3 fundamental domains of therapeutics being developed and explored: small molecules such as Talabostat and DPP4 Inhibitors, Antibody conjugate strategies such as immunotoxins, and immunotherapy by which adoptively transferred FAP-specific re-directed T cells are utilized.

Table 1

Representative studies of FAP and clinical outcomes in cancer

Cancer Type	Clinical Associations	Refs.
Gastric Carcinoma	Decreased overall survival	[51–53,76,99,100]
	Increased tumor grade and metastasis	
	Increased cancer cell invasion and migration	
Colorectal Carcinoma	Decreased overall survival	[51,82,83]
	Increased tumor growth, grade, and metastasis	
Ovarian Carcinoma	Decreased overall survival	[51,101]
	Increased tumor grade, metastasis, and probability of recurrence	
Pancreatic Adenocarcinoma	Decreased overall survival	[84,85,86]
	Increased tumor growth, grade, and metastasis	
	Increased cell cycle activation and tumor angiogenesis	
Lung Adenocarcinoma Oral Carcinoma	Decreased overall survival	[87]
	Decreased overall survival	[51,88]
	Increased tumor grade and metastasis	

Table 2

Putative FAP Substrates

Substrate	Standard Abbreviation	Type (UniProt)	Enzymatic Activity	Refs.
Neuropeptide Y	NPY	Neuropeptide/Signaling	Dipeptidyl-peptidase	[74,80,117]
Substance P	SP	Neuropeptide/Signaling	Dipeptidyl-peptidase	[74,80]
B-type Natriuretic peptide	BNP	Neuropeptide/signaling	Dipeptidyl-peptidase	[74,80,118]
Peptide YY	PYY	Neuropeptide/Signaling	Dipeptidyl-peptidase	[80,81]
α2-antiplasmin	A2-AP	Signaling (physiological)	Endopeptidase	[80,119–121]
Denatured type I and III collagens	COL1A1, COL3A1	Structural (physiological)	Endopeptidase/Gelatinase	[80,93,95,122,123]
Fibroblast growth factor-21	FGF-21	Signaling (physiological)	Endopeptidase	[124,125,160]
Glucagon-like peptide-1	GLP-1	Hormone/signaling	Dipeptidyl-peptidase	[126]
Glucose-dependent insulinotropic peptide	GIP	Hormone/signaling	Dipeptidyl-peptidase	[74]
ADAM15	ADAM	Structural (metalloproteinase)	Non-collagenous, dipeptidyl-peptidase	[50]
Interleukin-6	IL-6	Signaling (cytokine)	Non-collagenous, dipeptidyl-peptidase	[50]
Serine protease-23		Signaling	Non-collagenous, dipeptidyl-peptidase	[50]
Testican-1	SPOCK1	Structural	Non-collagenous, dipeptidyl-peptidase	[50,76]
Fibrillin-2	FBN2	Structural	Non-collagenous, dipeptidyl-peptidase	[76]
Matrilin-3	MATN3	Structural	Non-collagenous, dipeptidyl-peptidase	[50]
Extracellular matrix protein-1	ECM1	Signaling	Endopeptidase	[76]
Lysyl oxidase homolog-2	LOXL-2	Signaling	Deipeptidyl-peptidase	[76]
CXC-motif chemokine-5	CXCL5	Signaling	Dipeptidyl-peptidase	[76]
C1q tumor necrosis factor-related protein 6	CTRP6		Dipeptidyl-peptidase	[76]
TGFβ Latency Associated Peptide	LAP	Structural	unknown	[50]
LTBP-1, −2, and −4	LTBP	Signaling/Structural	unknown	[75,76,127]

Table 3

In silico analysis of microRNA (miR) targeting FAP mRNA Transcript and Associations with Cancer and HF

miR	miTG score	Cancer Associated miR	HF Associated miR
hsa-miR-3116	0.9972	[177]	–
hsa-miR-30e-5p	0.9933	[178,179]	[180]
hsa-miR-30b-5p	0.9790	[181]	[182]
hsa-miR-1254	0.9786	[183]	[184,185]
hsa-miR-30a-5p	0.9753	[186]	[187]
hsa-miR-30d-5p	0.9732	[188,189]	[190]
hsa-miR-6828–3p	0.9695	[191]	–
hsa-miR-6748–5p	0.9658	[191]	–
hsa-miR-7159–3p	0.9632	–	–
hsa-miR-30c-5p	0.9582	[192,193]	[194]
hsa-miR-335–3p	0.9565	[195,196]	[197,198]
hsa-miR-452–3p	0.9542	[199]	–
hsa-miR-3915	0.9526	[200]	[201]
hsa-miR-4689	0.9520	[202]	–
hsa-miR-4775	0.9450	[203,204]	–
hsa-miR-4526	0.9416	–	–
hsa-miR-676–5p	0.9385	–	–
hsa-miR-6745	0.9348	[205]	–
hsa-miR-141–3p	0.9319	[206,207]	[208]
hsa-miR-200a-3p	0.9254	[209,210]	[211–213]
hsa-miR-5194	0.9184	[214]	–
hsa-miR-6719–3p	0.9150	–	–
hsa-miR-330–3p	0.9131	[215,216]	[217,218]
hsa-miR-661	0.9077	[219]	–

miTG Score,miRNA target gene score; –, denotes no evidence found In-silico mapping performed using miR target prediction algorithm [223,224]

Table 4

Representative Clinical Studies and Trials for the FAP inhibitor Talabostat

Clinical Trial	Outcomes	Refs.
Pharmacodynamic up-titration of talabostat in pediatric patients	Well tolerated and computed dosing regimen developed	[246]
Phase I trial of single-dose talabostat in healthy male volunteers	Well tolerated, dose-related inhibition of plasma DPP-IV activity (as surrogate for FAP), increased plasma IL-6 levels	[247]
Phase I trial of multiple-dose talabostat in healthy male volunteers	Well tolerated, enhanced inhibition of plasma DPP-IV (as surrogate for FAP), increased plasma IL-6 and G-CSF	[243]
Phase I trial of talabostat and myelosuppressive chemotherapy in patients with solid tumor malignancy	Reduced chemotherapy related side effects, enhanced neutrophil recovery, enhanced cytokine regulation (IL-6, G-CSF, and IL-8)	[248]
Phase I trial of talabostat/rituximab for treatment of non-Hodgkin's lymphoma	Well tolerated as combination therapy (talabostat/rituximab); 3 partial responses (n = 20)	[243]
Phase II trial of talabostat for treatment of metastatic colorectal cancer	Evidence of FAP inhibition, minimal anti-tumor activity in metastatic colorectal cancer	[249]
Phase II trial of talabostat for treatment of stage IV melanoma	Evidence of some antitumor activity; 2 partial responses, 1 complete response (n = 31)	[250]
Phase II trial of talabostat/cisplatin for treatment of stage IV melanoma	Unable to show enhanced clinical activity of cisplatin; 6 partial responses (n = 43)	[251]
Phase II trial of talabostat/docetaxel for treatment of stage IIIB/IV NSCLC	Unable to show enhanced clinical activity of docetaxel; 2 partial responses, 1 complete response (n = 42)	[252]
Phase III trial of talabostat/docetaxel for treatment of advanced NSCLC	Terminated - increased mortality in intention to treat group	[253]
Phase II trial of talabostat/pembrolizumab for treatment of advanced solid cancers	Active, not recruitiing - evaluate effects of talabostat on various immunological effector cells, notably cancer associated fibroblasts	[254]
Phase 0 trial of talabostat and gemcitabine in patients with advanced pancreatic cancer	Assess initial safety and 6 month outcomes. Study terminated.	[255]