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Focal adhesion kinase signaling in cardiac hypertrophy and failure

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Focal adhesion kinase (FAK) is a broadly expressed tyrosine kinase implicated in cellular functions such as migration, growth and survival. Emerging data support a role for FAK in cardiac development, reactive hypertrophy and failure. Data reviewed here indicate that FAK plays a critical role at the cellular level in the responses of cardiomyocytes and cardiac fibroblasts to biomechanical stress and to hypertrophic agonists such as angiotensin II and endothelin. The signaling mechanisms regulated by FAK are discussed to provide insight into its role in the pathophysiology of cardiac hypertrophy and failure.

Key words: Focal adhesion kinase; Mechanical signaling; Cardiovascular system; Signal transduction

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Introduction

Adult heart translates sustained increases in workload in pathological conditions such as hypertension, valvular heart diseases and myocardial infarction into reactive increases of myocardial mass (i.e., reactive hypertrophy). Although reactive hypertrophy is initially adaptive, after a time, it causes maladaptive effects that eventually set the stage for heart failure. At the cellular level, myocardial hypertrophy is the consequence of an increase in cardiomyocyte size. Mechanical forces that are generated as a consequence of hemodynamic stress are thought to be the primary stimuli for the reactive hypertrophy of cardiomyocytes. However, there is much evidence showing a link between concurrent increases in neural or hormonal factors (e.g., norepinephrine, angiotensin II) and the reactive hypertrophic growth of cardiomyocytes in pathological conditions. Notably, when stimulated by continuous mechanical stress and neuro-hormonal factors, hypertrophic cardiomyocytes develop pathologic features and eventually die. In addition, the connective tissue stroma increases in excess of the apparent need, leading, together with cardiomyocyte degeneration, to myocardial dysfunction. The stimulation of cardiomyocytes and cardiac fibroblasts by mechanical stress and neurohormonal factors activates multiple signal transduction cascades, which ultimately affect nuclear factors that regulate gene expression and hypertrophic growth. Many signaling pathways of cardiomyocytes that are associated with reactive hypertrophy have been also found to be activated in maladapted hypertrophic hearts, the difference being that there is an exaggeration of their activities in failing hearts compared to those observed in adapted hypertrophy (1). In this review, we focus on the regulation of focal adhesion kinase (FAK), an intracellular tyrosine kinase, in cardiomyocytes and consider its role in reactive hypertrophy and failure.

The structure and mechanisms of focal adhesion kinase regulation

FAK plays a pivotal role in important aspects of cell behavior such as migration, proliferation, growth, and sur-

vival. In many cell types FAK is recruited primarily to sites of integrin clustering where it is activated by undefined mechanism(s). The pleiotropic effects of FAK on cells are mediated by the mobilization of multiple signaling pathways, issues that have been the topic of excellent reviews (2,3) and will not be discussed in detail here.

FAK is a 125-kDa protein tyrosine kinase composed of an N-terminal FERM (protein 4.1, ezrin, radixin and moesin homology) domain, followed by an ~40 residue linker region, a central kinase domain, a proline-rich low-complexity region, and a C-terminal focal-adhesion targeting domain (Figure 1A) (2). The crystal structure of the FERM/catalytic domain complex (4) suggests that FAK is maintained in an autoinhibitory conformation by an intra-molecular interaction between the FERM and the catalytic domain that blocks the active site of the catalytic domain inhibiting access to the ATP and substrate-binding sites as depicted in the scheme shown in Figure 1B. When FAK is activated, Tyr397 within the linker region between the FERM and the catalytic domain is exposed by conformational changes and autophosphorylated, with the consequent creation of a high-affinity binding site for the Src homology 2 domains of Src family kinases (5). Accordingly, mutations introduced in a patch of residues comprising Y180 through M183 located at the bottom of the FERM

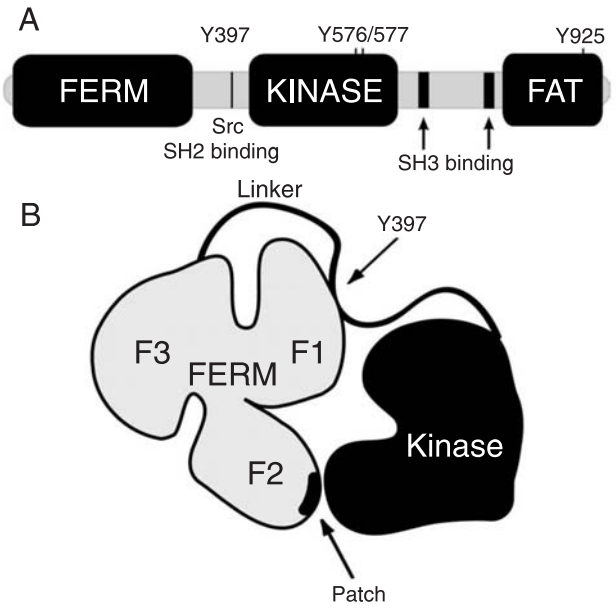

Figure 1. *A*, Domain structure of focal adhesion kinase (FAK). Src interaction site and key tyrosine phosphorylation sites are indicated. *B*, Schematic presentation of auto-inhibited FERM/catalytic domain derived from crystal structure. FAT = C-terminal focal-adhesion targeting domain; FERM = protein 4.1, ezrin, radixin and moesin homology.

F2 lobe disrupt the FERM/catalytic domain interface and markedly increase FAK catalytic activity (4,6). However, the mechanisms responsible for FERM domain release from the catalytic domain in cells remain elusive. It is suspected that an activating protein, presumably docked in the FERM domain, might be responsible for disrupting the FERM/kinase interface and activation of FAK (4). Candidate proteins include the cytoplasmic regions of β-integrin or epidermal growth factor receptor, but cytosolic ligands may also exist. More recently (7), studies performed with a fluorescence resonance energy transfer-based FAK biosensor used to probe FAK conformational change in live cells showed that FAK activation may be mediated by interaction of phosphatidylinositol 4,5-bisphosphate with a basic patch of the FERM F2 lobe. This patch (KAKTLRK) comprises amino acids K216 through K222 located on the surface of the FERM/catalytic domain complex. Mutation-based studies have identified this patch as a key motif for FAK activation *in vivo* in response to cell adhesion (8).

Once phosphorylated, Tyr397 sites recruit and activate Src. The interaction between Tyr397-phosphorylated FAK and Src leads to a cascade of tyrosine phosphorylation of multiple sites in FAK (residues Tyr576, Tyr577, and Tyr925) (9,10), as well as in other signaling molecules such as the 130-kD adaptor protein Crk-associated substrate (p130Cas) (11) and paxillin (12). Active FAK can also affect the organization of the actin cytoskeleton via Rho-family GTPases and other downstream signaling pathways (3), including Ras and the mitogen-activated protein kinases ERK1/2 (13). Furthermore, phosphorylation of Tyr397 also appears to be important for the recruitment of other SH2-containing proteins, including the 85-kDa subunit of phosphoinositide-3-kinase (PI3K), which can promote activation of AKT, a serine kinase involved in the regulation of energetic metabolism, cell growth and survival (14,15).

Localization and regulation of FAK in cardiomyocytes

FAK is highly expressed in cardiomyocytes, has a relatively low basal level of activity and is promptly activated by mechanical stimuli (16-19) as well as by agonists such as endothelin and angiotensin II (20,21). While the spatial distribution of FAK in cardiomyocytes provides some insight into the mechanisms responsible for its activation in this particular cell type, this matter remains largely unclear. Immunohistochemistry and immunoelectron microscopy using FAK-specific antibody were used to investigate the localization of FAK in adult and neonatal rat

ventricular cardiomyocytes (17,18,22,23). It is important to mention that, despite some phenotypic differences, neonatal rat ventricular cardiomyocytes simulate the responses of adult animal *in vivo* with reasonable accuracy and have been extensively used to identify potential signaling pathways involved in hypertrophy. Cardiomyocytes double-labeled with anti-FAK antibody and phalloidin (a marker for actin) showed anti-FAK fluorescent staining to be regularly distributed in register with the myofilaments preferentially in the sarcomeric A-bands, as well as in the perinuclear region (Figure 2A-C) (23). The location of FAK in the sarcomeric A-bands was confirmed by the overlap between anti-FAK and anti-myosin fluorescence as well as by immunoelectron microscopy imaging (23). Interestingly, the spatial distribution of FAK in cardiomyocytes was shown to vary in response to mechanical stress. In mechanically stimulated cardiomyocytes, FAK-specific immunofluorescence did not overlap the A-band but rather the I-band, suggesting that mechanical stress induces FAK relocation to distinct sites of cardiomyocytes (17,23). Indeed, anti-FAK immunogold staining was detected preferentially as aggregates close to Z-discs and costameres in cardiomyocytes from the overloaded rat left ventricle. In addition to mechanical stress, FAK also undergoes translocation and activation in response to agonists that activate Gq-coupled receptors (20,24). In this context it is important to mention that stretch-induced release of angiotensin II and endothelin-1 from cardiomyocytes and/or non-muscle cells may also indirectly activate FAK in cardiomyocytes. Moreover, consistent with the imaging data, studies conducted with yeast-two hybrid screening of a rat left ventricle cDNA library with a FERM/catalytic domain construct and pull down assays indicated that FAK interacts with a C-terminal region of myosin, possibly through a direct binding in the FAK FERM domain (23). Remarkably, FAK/myosin interaction was observed in non-stimulated cardiomyocytes but not in cells that were subjected to mechanical stress (23). Together, cardiomyocyte imaging and biochemical data raise the interesting possibility that FAK quiescence in non-stimulated cardiomyocytes may depend on its interaction with myosin in sarcomeric A-bands. In turn, FAK activation might be dependent on its dissociation from myosin, relocation and clustering at costameres and Z-disks. The mechanisms responsible for the dissociation of FAK from myosin, its relocation as well as their meaning for FAK activation in cardiomyocytes remain unclear. It could be that FAK relocation and clustering at sites such as Z-discs and costameres may optimize FAK signaling because of the location at strategic sites that convey mechanical stimuli as well as because the molecular proximity in clusters may serve to enhance and sustain FAK signaling. This agrees with data from studies (25) performed in distinct cell types indicating that FAK clustering enhances and sustains FAK activation, allowing the recruitment and activation of additional cellular signaling molecules such as those involved in the activation of growth and survival pathways. Still in this context, it is important to mention that several mechanisms have been shown to modulate FAK activity in cardiomyocytes, possibly by interfering in the ability of FAK to interact with myosin or even by modulating the efficiency of the mechanisms responsible for its relocation in the cells. For instance, FAK activation in cardiomyocytes either by stretch or endothelin has been demonstrated to be highly dependent on the upstream activation of RhoA/ROCK, perhaps mediated via local alterations in the actin cytoskeleton at or near sites of integrin clustering (18,26). Moreover, there is also evidence to indicate that protein kinase C epsilon (PKCε) is directly involved in FAK activation. PKCε co-localizes with FAK in focal adhesions and is involved in the endothelin-induced activation of FAK in cardiomyocytes (26). PKCε also seems to regulate FAK via signaling pathways involved in local changes in the actin cytoskeleton. Finally, tyrosine phosphatases provide an additional level for regulating FAK phosphorylation and activity in cardiomyocytes. Recently, we demonstrated that Shp2, a tyrosine phosphatase, may exert a critical function in controlling FAK activity in non-stimulated cardiomyocytes (27). FAK activity is enhanced in non-stimulated cardiomyocytes depleted of Shp2, indicating that depletion of Shp2 is sufficient to bypass the mechanisms that activate the FAK/Src complex by biomechanical stress and soluble factors. The data suggest the possibility that FAK and Shp2 may form a complex that regulates the basal phosphorylation status of FAK in cardiomyocytes. Furthermore, reduction of Shp2 activity toward FAK seems to play a permissive role in the activation of FAK induced by biomechanical stimuli in cardiomyocytes, suggesting that FAK activation by me-

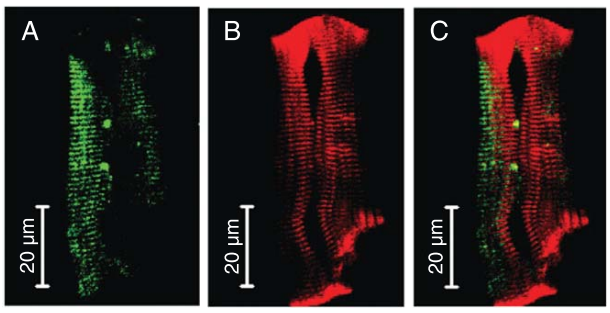

Figure 2. Ventricular adult cardiomyocyte fluorescent imaging. *A*, Anti-focal adhesion kinase (FAK) staining in green. *B*, Phalloidin staining in red. *C*, Merge anti-FAK/phalloidin.

chanical stress in cardiomyocytes may depend on down-regulation of Shp2 phosphatase activity and dissociation of FAK from Shp2. Interestingly, Shp2 activity was demonstrated to be markedly increased when RhoA is down-regulated or stress fibers are disrupted (28-30). Yet, binding of Src to FAK reduces the susceptibility of FAK to tyrosine phosphatases (31). These data suggest the possibility that FAK/Src association, activation of RhoA/ROCK signaling and rearrangement of cytoskeletal proteins might reduce FAK susceptibility to Shp2 phosphatase activity, tune-down Shp2 catalytic activity and promote dissociation of FAK from Shp2, contributing to the activation of the FAK/Src complex in stretched cardiomyocytes

Interestingly, in cardiomyocytes subjected to prolonged stimulation by mechanical stress FAK also relocates to the nucleus (23,32,33). The role of FAK in the nucleus of cardiomyocytes is still unclear, but it has been suspected to regulate chromatin structure, transcription, mRNA processing, and nuclear export (32). Recent studies in non-myocyte cells have shown that FAK interacts with and sequesters p53 in the nucleus of cells (34,35). This interaction is thought to facilitate the proteolysis of p53 by Mdm2, which causes the ubiquitination and degradation of p53. These effects were demonstrated to be anti-apoptotic. Therefore, FAK is proposed to be a critical scaffold protein that sequesters proapoptotic proteins, such as p53, to mediate cell survival. However, this issue remains unexplored in cardiomyocytes.

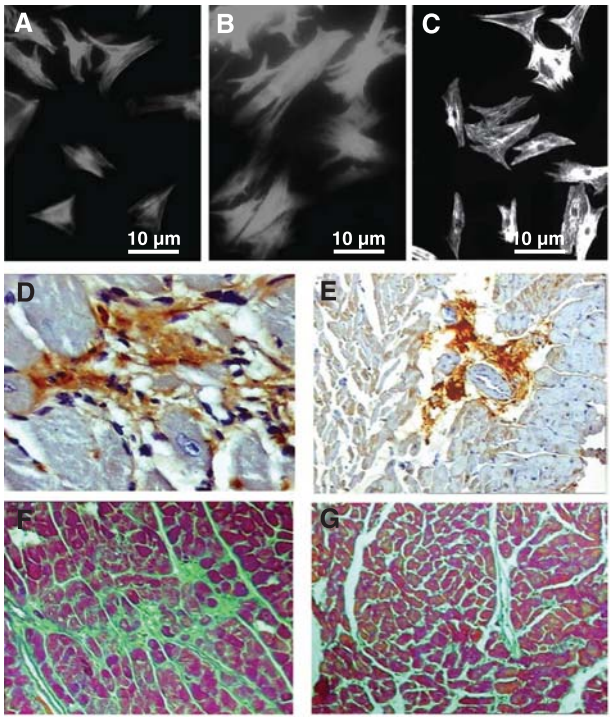

Figure 3. Focal adhesion kinase (FAK) depletion impairs the hypertrophic responses of cardiomyocytes to mechanical stress (*A*, non-stimulated; *B*, stretched - 24 h; *C*, depleted of FAK and stretched cardiomyocyte; bar = 10 µm for panels A-C). *D*, High magnification (1200X) of anti-FAK myocardial staining (yellowish) from 12-week banded mice highlighting an area of focal myocardial fibrosis. *E*, Low magnification (400X) of anti-FAK staining from a myocardial biopsy taken from a patient with heart failure due to mitral regurgitation. *F*, Low magnification (400X) of Masson trichrome staining (green) from 6-week banded mice treated with an irrelevant small interfering RNA (siRNA) targeted to green fluorescent protein. *G*, Low magnification (400X) of Masson trichrome staining from a 6-week banded mouse treated with siRNA targeted to FAK.

FAK and cardiac development and hypertrophy

Cardiomyocytes withdraw irreversibly from the cell cycle soon after birth and subsequent growth in this particular cell type occurs predominantly through hypertrophy rather than hyperplasia. While several lines of evidence support a role for FAK in cardiomyocyte hypertrophy, more recently studies have also implied the participation of FAK in cardiogenesis and in cardiomyocyte proliferation during embryonic development (36-38). Studies using cultured cardiomyocytes demonstrated that FAK overexpression up-regulates the hypertrophic gene markers (39), suggesting that FAK may be sufficient to induce hypertrophy, but it remains unknown whether it is sufficient to induce a complete hypertrophic phenotype of cardiomyocytes. In addition, FAK has also been shown to be necessary for the up-regulation of cardiomyocyte hypertrophic gene markers to biomechanical stress and to agonists such as phenylephrine and endothelin (17-21). Recent studies performed in cardiomyocytes depleted of FAK confirmed the importance of FAK to the hypertrophic growth that occurs in response to biomechanical stress (27) (Figure 3A-C). Interestingly, however, depletion of FAK does not affect the phenotype of non-stimulated cardiomyocytes, suggesting that FAK is not necessary for the maintenance of cardiomyocytes basally.

The studies on the cardiomyocyte model system have also contributed to clarify the signaling pathways downstream to FAK. Multiple downstream pathways are proposed to mediate the effects of FAK in cardiomyocytes. For instance, activation of mitogen-activated protein tyrosine kinases has been attributed a role in mediating the pro-hypertrophic effects of FAK. Studies have shown that activation of ERK1/2 in response to hypertrophic agonists may be mediated by FAK (16,22). Of note, the early activation of ERK1/2 has been suggested to contribute to the

expression of fetal genes (e.g., atrial natriuretic factor, ß-myosin heavy chain, and skeletal muscle α-actin) and hypertrophy in cardiomyocytes (40). In addition, FAK can also regulate the JNK/c-Jun pathway, which in turn plays an important role in the regulation of the atrial natriuretic factor promoter activity and the immediate early genes induced by cyclic stretch (19). However, the relative importance of ERK1/2 and JNK to the pro-hypertrophic effects mediated by FAK remains unclear. Studies in cardiomyocytes also revealed that MEF2 transcription factors, which are master regulators for several sarcomeric and regulatory proteins in cardiomyocytes, are also critical downstream effectors to FAK signaling. However, the intermediate signaling pathways that connect FAK signaling to MEF2 are still unknown (19). Recent studies have revealed the importance of the AKT/mammalian target of rapamycin (mTOR) pathway as a mediator of FAK pro-hypertrophic effectors (27). FAK activation induced by depletion of Shp2 or by cyclic stretch was demonstrated to be linked to AKT and mTOR activation. Pharmacological inhibition with the specific mTOR inhibitor rapamycin suppressed cardiomyocyte hypertrophy induced by Shp2 depletion or biomechanical stress, highlighting a potentially critical role for AKT and mTOR as downstream mediators of the pro-hypertrophic actions of FAK signaling. Interestingly, FAK has been demonstrated to control AKT via interaction with the p85 subunit of PI3K (16,41), and AKT regulates mTOR primarily through the phosphorylation of TSC2 at Thr1462 (42). FAK also directly interacts with and inhibits TSC2, thereby regulating the mTOR pathway (43). An increase in cardiomyocyte size has been observed following the stimulation of AKT by the upstream activator of PI3K and after inhibition of PTEN, the enzyme that degrades inositol 3,4,5-trisphosphate (44). In addition, a constitutively active mutant of AKT increases cardiomyocyte size. The hypertrophy caused by the expression of active AKT is attenuated by rapamycin, which indicates that mTOR is the principal effector (45). Rapamycin also blocks left ventricular hypertrophy induced by mechanical stress (45).

Many of the molecules and mechanisms that regulate growth in the adult heart in response to stress signals that provoke cardiac hypertrophy seem to also contribute to cardiac development (46). A role for FAK in cardiac development and hypertrophy was recently highlighted by the use of FAK loss-of-function models. Total deletion of FAK in the mouse embryo induces early embryonic lethality with mesoderm and cardiovascular development defects (47,48). Neither a normal heart nor fully developed blood vessels were present in the FAK-null embryos. The role of FAK in cardiac development was examined in cardiac-specific conditional knockout (38) produced by crossing floxed FAK mice with MLC2a-Cre transgenic mice, a transgene that is efficiently expressed in embryonic heart. These mice showed high embryo lethality and heart developmental defects characterized by muscular ventricular septal defect and thin ventricular wall that contained only a small number of loosely packed cells in the compact and trabecular zone. Furthermore, the number of Ki67 and troponin T double-positive cells in embryos depleted of FAK was significantly decreased compared with the control, suggesting a defect in embryonic cardiomyocyte proliferation as the cause of cardiac defects in this model. However, a distinct mouse model of embryonic deletion of floxed FAK directed by *nkx2-5*-Cre showed no change in the ability of cardiomyocytes to proliferate or survive, although it confirmed the importance of FAK for the proper embryonic development of outflow tract and ventricular septation (37). The reason for the differences in the effects of embryonic FAK on cardiomyocytes is unclear but may be attributed to the differences in the cardiac specificity and efficiency of the promoters used to drive the recombinase in the two studies. Still regarding this issue, it is important to mention that FAK has been demonstrated to be an important factor for cell proliferation and differentiation of skeletal muscle myoblasts (49,50). Moreover, studies performed in mouse embryonic stem cells have demonstrated that FAK signaling is a key negative regulator of cardiogenesis (36).

FAK loss-of-function models were also used to explore its role in cardiac hypertrophy (51-53). While the various models presented discrepant results, they generally confirmed the assumption that FAK is required for the proper response of the heart to hypertrophic stimuli, although it is not required for the maintenance of basal myocardial architecture. Peng et al. (51) generated ventricular cardiomyocyte-specific FAK-null mice by deleting floxed FAK (loxP sites flanked exon 3 of FAK gene) directed by MLC2v-Cre, which is efficiently expressed during the postnatal period. Cardiac-specific reduction of FAK protein level was observed 2 weeks after birth. The deletion of FAK in cardiomyocytes did not affect basal cardiac function or structure, but left ventricular chamber dimensions, the heart/body weight ratio and the levels of hypertrophic genetic markers were increased in FAK knockout mice after transverse aortic constriction or infusion of angiotensin II, compared with the control littermates. Furthermore, FAK knockout mice but not control mice showed multifocal interstitial fibrosis in the myocardium. In contrast with these findings, another lineage of cardiac-specific FAK knockout mice (loxP sites flanking exon 20; directed by MLC2v-Cre; maximal FAK depletion by the 3rd month after birth) (52) showed a mild to moderate attenuation of

reactive hypertrophy and hypertrophic gene markers to aortic constriction, although, similar to the model developed by Peng et al. (51), no change was found in basal structure or function of the left ventricle in their FAK knockout mice. Enhanced perivascular fibrosis was also observed following aortic constriction in FAK-depleted hearts. The reason for the discrepancies between the two models of FAK cardiac-specific knockout is unclear, but might be related to differences in the period necessary to achieve the maximal depletion of FAK (2 weeks and 3 months) and the timing and intensity of hypertrophic stimuli used in the two studies. More recently, by using a model of FAK silencing induced by RNA interference strategy, we demonstrated that transient FAK depletion (80%) markedly attenuated the development and reversed already-established left ventricular hypertrophy in aortic-banded mice (53). This implies that FAK is necessary not only to the development but also to sustain left ventricular hypertrophy in response to chronic pressure overload. The marked effects of FAK depletion induced by gene silencing in comparison to those seen in FAK cardiac-specific knockout mice might be related to the fact that this strategy induces a broad depletion of FAK in the myocardium, namely cardiomyocytes, fibroblasts and cells from blood vessels.

FAK signaling and heart failure

Evidence is emerging implicating FAK signaling in the development of hypertrophy maladaptation. Increases in FAK levels and activity were demonstrated in dysfunctional chronically overloaded rat left ventricle (54). There was a high correlation between the degree of hypertrophy and FAK expression during the transition from compensatory left ventricular hypertrophy to heart failure. Remarkably, although FAK was detected in cardiomyocytes of both sham and banded rats, much of the increased FAK expression appeared to occur in the cardiac interstitium, suggesting that the increased FAK expression in the cardiac interstitium was derived from proliferating cardiac fibroblasts. However, in this model FAK was also shown to be increased in some cardiomyocytes adjacent to areas of fibrosis, implying that activation of FAK in cardiomyocytes may also contribute to the deterioration of chronically overloaded rat heart. Similar results were obtained for chronically overloaded mouse left ventricle (53) (Figure 3D). In addition, FAK expression and activity were also demonstrated to be increased in myocardial samples taken during cardiac surgery from subjects with mitral regurgitation hearts as compared to samples from cardiac transplantation donor hearts (55). Remarkably, although in myocardial samples from donor hearts FAK was detected almost exclusively restricted to cardiac myocytes, in samples from failing hearts FAK was found to be located in cardiomyocytes and in the myocardial interstitium (Figure 3E). A positive correlation was found between collagen and the interstitial areas stained with the anti-FAK antibody. Moreover, the areas stained with FAK were shown to be coincident with fibroblasts, indicating that most of the interstitial FAK was located in fibroblasts. These data agree with our recent demonstration that fibroblasts harvested from the left ventricles of 7-day banded mice had increased FAK expression (53). Moreover, it was shown that FAK silencing markedly attenuated the interstitial fibrosis (Figure 3F,G), strengthening the notion that FAK plays a critical role in the myocardial fibrogenesis induced by chronic pressure overload. Indeed, myocardial FAK silencing was shown to be accompanied by attenuation in the rises of myocardial collagen and MMP-2 activity, and, importantly, it was also demonstrated that FAK silencing in fibroblasts harvested from overloaded myocardium was accompanied by a reduction in MMP-2 expression, a molecule that has been shown to be a major determinant of the extracellular matrix remodeling process in overloaded myocardium (56). Further morphological and echocardiographic analysis indicated that FAK silencing also mitigated the ongoing structural and functional deterioration of the hypertrophic mouse left ventricle. While these data support a role for FAK signaling in the deterioration of chronically overloaded heart, they are apparently in conflict with the observations in cardiomyocyte-restricted knockout mice that have indicated that depletion of FAK predisposes to a premature maladaptive remodeling of chronically overloaded hearts. We postulate that such apparently contradictory effects might be related to the fact that myocardial FAK silencing, in contrast to the myocyte-restricted knockout, may attenuate the development of fibrosis by lowering FAK expression in fibroblasts, in addition to cardiac myocytes, favoring a better outcome of chronically overloaded left ventricles. Still in the context of myocardial deterioration it is worth mentioning that FAK activation has been implicated in the expression of hypertrophic markers by cardiomyocytes, which are thought to be associated with deterioration of the myocardium (17-19,53). This implies that activation of FAK may be important to activate signaling pathways involved in pathologic hypertrophy of cardiomyocytes. Thus, it is conceivable that the persistently activated FAK signaling both in fibroblasts and in cardiomyocytes may be detrimental to the hypertrophied left ventricle.

Conclusion

FAK regulates the response of cardiomyocytes to biomechanical stress and hypertrophic agonists such as an-

giotensin II and endothelin. The mechanisms of FAK activation by biomechanical stress and the downstream pathways involved in FAK signaling have begun to be unraveled. The importance of FAK signaling in cardiac pathophysiology is not restricted to its effects in cardiomyocytes but is also important in fibroblasts and possibly in cells from myocardial vessels. FAK loss-of-function models have recently provided data that confirm the role of FAK in cardiac embryonic development and hypertrophy, and have also indicated that the persistent activation of FAK may contribute to the deterioration of chronically overloaded hearts. However, we still lack a complete view of how FAK is activated by mechanical forces, as well as how the various signaling mechanisms downstream to FAK are integrated and can influence the pathophysiology of cardiac hypertrophy and failure.

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