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ErbB/integrin signaling interactions in regulation of myocardial cell-cell and cell-matrix interactions

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Abstract

Neuregulin(Nrg)/ErbB and integrin signaling pathways are critical for the normal function of the embryonic and adult heart. Both systems activate several downstream signaling pathways, with different physiological outputs: cell survival, fibrosis, excitation-contraction coupling, myofilament structure, cell-cell and cell-matrix interaction. Activation of ErbB2 by Nrg1β in cardiomycytes or its overexpression in cancer cells induces phosphorylation of FAK (Focal Adhesion Kinase) at specific sites with modulation of survival, invasion and cell-cell contacts. FAK is also a critical mediator of integrin receptors, converting extracellular matrix alterations into intracellular signaling. Systemic FAK deletion is lethal and is associated with left ventricular non-compaction whereas cardiac restriction in adult hearts is well tolerated. Never the less, these hearts are more susceptible to stress conditions like trans-aortic constriction, hypertrophy, and ischemic injury. As FAK is both downstream and specifically activated by integrins and Nrg-1β, here we will explore the role of FAK in the heart as a protective factor and as possible mediator of the crosstalk between the ErbB and Integrin receptors.

Keywords

Neuregulin; Nrg1β; FAK; Integrin; cardiomyocytes; heart

2. Introduction

In 1995 three articles were contemporaneously published in Nature describing the effect of systemic deletion of Neuregulin(Nrg)-1, epidermal growth factor receptors ErbB2 and ErbB4 in mice. These studies demonstrated that Nrg/ErbB signaling is needed for the correct development of heart trabeculae, a structure responsible for the normal function of the embryonic heart[1–3]. Since then our knowledge has greatly increased and it is

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now clear that this signaling system is also active in the adult heart and is critical for its maintenance under stressed conditions. Specific deletion of ErbB2[4] and ErbB4[5] leads to spontaneous dilated cardiomyopathy associated with higher susceptibility to aortic banding. Both cardiac and cancer research have connected directly and indirectly Nrg-1β/ErbB to several signaling pathway, such as Phosphatidylinositol 3-Kinase (PI3K)/Akt, Mitogen-Activated Protein Kinase (MAPK)/ Extracellular signal-Regulated Kinase (Erk) 1/2, and the non-receptor tyrosine kinase Src/Focal Adhesion Kinase (FAK), and demonstrated its involvement in a wide variety of physiological outputs, including cardiac cell survival, migration, angiogenesis, cytoskeleton, and excitation contraction coupling(for a detailed review on these pathways in the heart see ref. [6]).

The primary role of integrins is to link the extracellular matrix (ECM) to the intracellular signaling. Deletion of β1 subunit, the most common in the heart, suggests that ECM is involved in the differentiation of cardiomyocytes during heart development [7]. Integrins are also critical for the maintenance of the adult heart both under normal and pathological conditions, as their deletion results in a spontaneous increase in fibrosis as well as induction of heart failure [8]. The non-receptor tyrosine kinase FAK is the main effector of integrins, converting changes in the extracellular matrix into intracellular signaling.

As FAK is both downstream and specifically activated by integrins and Nrg-1β, here we will explore the role of FAK in the heart as a protective factor and a possible mediator of the crosstalk between ErbB and Integrin receptors (Fig 1).

3. Nrg-1β/ErbB2/ErbB4 signaling

3.1 Nrg-1β/ErbB dependent Akt and Erk1/2 signaling and their role in the heart.

Both Erk1/2 and Akt signaling pathways have been extensively studied in the heart and we will just briefly summarize these studies here (for a detailed review on these pathways as NRG-1β downstream effectors please refers to Pentassuglia and Sawyer, 2009, Experimental Cell Research: The role of Neuregulin-1β/ErbB signaling in the heart[6]). Several studies conducted so far demonstrate that both Erk1/2 and Akt mediate Nrg1β-dependent cell survival, metabolism, and growth in the heart under normal and stressed conditions. Postnatal cardiac-specific deletion of ErbB2 leads to spontaneous dilated cardio-myopathy and a higher susceptibility to stress stimuli [4]. Cardiac-specific deletion of both Grb2-associated binder (GAB) [9, 10] 1 and 2, scaffolding adaptor proteins that mediates Nrg1β/ErbB signaling, abolishes Nrg-1β induced phosphorylation of both Erk1/2 and Akt. Concomitantly these hearts show profound dilated features associated with deposition of both collagen and elastic fibers, and alterations at the cardiac vessels [9].

There is growing evidence that the Nrg-1β/ErbB2 signaling plays a critical role in conditions of stress. *Ex-vivo* ischemia reperfusion of isolated hearts in the Langendorff system induces Nrg-1β cleavage, activation and phosphorylation of the ErbB4 receptor and downstream signaling pathways. These data suggests that the ErbB receptors are possibly involved in cardiac recovery[11]. Nrg-1β preconditioning attenuates apoptotic cell death during ischemic injury as shown by a decrease in cleaved caspase-3 and an increase in the phosphorylation levels of Akt. Concomitant inhibition of PI3K signaling was able to

block Nrg-1β-dependent cardioprotection [12]. In isolated adult myocytes pretreatment with Nrg-1β prevents doxorubicin-induced cell death. Akt inhibition blocks this effect, whereas a constitutively active form of Akt exerts a function similar to Nrg-1β itself [13]. Akt also mediates Nrg-1β/ErbB protection against reactive oxygen species (ROS). Nrg-1β pretreatment significantly decreases ROS in cultured myocytes treated with hydrogen peroxide, while inhibition of Akt abolishes this effect [14]. In mice treated with doxorubicin, Nrg-1β promotes survival and preservation of cTnI and cTnC from degradation in the heart via Akt signaling [15], further proving a critical role for Akt in Nrg-1β/ErbB-dependent survival.

Erk1/2 signaling activated by Nrg-1β has been implicated in the promotion of cardiomyocyte differentiation from embryonic stem cells. During the development of embryonic bodies there is a distinctive pattern of ErbB receptor expression. All cells of the embryonic body express ErbB2 but only the myocyte fraction expresses ErbB4, which is essential for their development and survival[16]. ErbB induced cardiomyocyte development requires the activation of Erk1/2, as the expression of either wild type or constitutively active MEK1 is sufficient to increase the number of cells expressing myosin heavy chain [17]. In both neonatal and adult myocytes, Erk1/2 mediates Nrg-1β-dependent hypertrophy, protein expression, and sarcomere structure [18–20]. The inhibition of ErbB2 or Erk1/2 leads to myofilament disarray both in adult and neonatal myocytes[18, 21]. These data support a role for the Nrg-1β/ErbB2/Erk1/2 signaling axis in the assembly and maintenance of the contractile apparatus in the heart.

3.2 Nrg-1β dependent FAK activation

FAK, a component of the Focal Adhesion Complex (FAC), interacts and regulates several structural and signaling proteins, including the Nrg-1β signaling pathway in the heart. FAK has three distinct domains: the N-teminal FERM (F for 4.1 protein, E for ezrin, R for radixin and M for moesin), which has autoinhibitory function[10, 22], a central kinase domain[23, 24], and a C-terminal Focal Adhesion Targeting (FAT) domain[25, 26]. The first step of FAK activation requires auto-phosphorylation of the tyrosine residues 397 induced by integrin activation (see paragraph 4.1). The FERM domain has an auto-inhibitory function and integrin activation leads to FAK binding to talin and paxillin via FAT. This induces conformational changes that lead to displacement of the FERM domain, releasing the autoinhibition; at this point FAK can autophosphorylate itself at Y397. This autophosphorylation induces Src binding and phosphorylation of Y576 and Y577 in the catalytic domain (Fig 1A) [27–29].

The different phosphorylation sites of FAK modulate either its own catalytic activity or the affinity for binding proteins. Phosphorylation of Y397 creates a motif recognized by SH2-domain containing proteins (PLCγ, SOCS, GRB7, P120, and p85 of PI3K)[30–33]. Phosphorylation at Y397 induces Src binding and activation of downstream signaling pathway through both FAK and Src[34] and promotes the recruitment of PI3K and p130CAS[33–36]. Src phosphorylation of FAK increases affinity for SH3-domain mediated binding of p130CAS and for SH2- domain mediated binding for CRB2 adaptor proteins[37, 38]. Y925 can also activate myosin light chain kinase via ERK2[39, 40]. The best-known

downstream targets of FAK are p130CAS and Paxillin. Recent experiments show that FAK plays a role in FAC dynamics and modulation[41] and promotes maturation of FAC with inhibition of α-actinin binding to actin filaments[42]. FAK localization at the Z-line suggests a role in sarcomere organization as well [43].

In isolated adult rat ventricular myocytes (ARVM) Nrg-1β is able to activate the Src/FAK signaling pathway. Nrg-1β treatment induces phosphorylation of FAK at Y861 and Y925 that is most prominent at the sites of the intercalated disk (Fig 1B). This is associated with formation of lamellipodia and ultimately cell-cell junctions[44]. This signal may mediate the cardioprotective role of Nrg-1β in stress conditions. In isolated hearts, ischemic injury leads to Nrg-1β cleavage and ErbB4 as well as FAK phosphorylation [11]. Evidence collected in other tissues shows similar findings. In the brain Nrg-1β induces FAK activation via ErbB2/ErbB3 heterodimer [45]. In different type of tumors (brain, breast, and ovary) positive for the ErbB2 receptor FAK is activated at baseline conditions [46–48] and promotes tumor cell motility [49–51], proliferation [52], formation of FAC [53, 54], resistance to ErbB2 specific chemotherapeutic agents [55].

3.3 Role of FAK in cardiac development

Cardiac morphogenesis is one of the first events that takes place during embryonic development and requires the complex coordination of recruitment, differentiation, and proliferation of cardiac and cardiac precursors cells. Like the Nrg/ErbB pathway[1–3], FAK signaling is involved in the embryonic development of the heart from its early stages. Systemic deletion of FAK in mice is lethal and shows cardiac defects in early embriogenesis as the heart fails to separate the mesocardial and the endocardial layers and lethality is associated with left ventricular non-compaction[56]. During heart development, a set of cells, the Neuronal Crest Cells (NCCs), migrate from the neuronal tube toward the developing heart to participate in the maturation of the cardiac outflow tract in to the aorta and pulmonary trunk. FAK expression is critical for the differentiation of the NCCs into smooth muscle cells (SMCs), which participate in the development of the aortic arch arteries. The failure of NCCs to develop in to SMCs results in the regression of the developing aortic branches rather than a premature halting of the process [57]. Embryonic myocyte chemotaxis is also impaired, suggesting the involvement of FAK in myocyte migration towards the cushion mesenchyme [58, 59]. Similar to what is observed in vivo, FAK regulates cardiogenesis and migration in cultured embryonic stem cells. Inhibition of FAK phosphorylation leads to decreased cell migration, which stimulates ES cells to differentiate in cardiac lineages, as assessed by expression of α-MHC [60]. Cardiac specific deletion of FAK with the use of nkx2.5 promotor-driven Cre-recombinase induces rapid cyanosis and mice die 10 to 120 min after birth. Analysis of the embryonic cardiac tissue shows that FAK is reduced as early as E13.5 and it is almost absent at E18.5. Histological analysis shows defect in ventricular septation and in few cases the presence of a double-outlet right ventricle, thickening of the semilunar valve leaflets but normal trabeculation[58].

Similar to what has been observed in nkx2.5-driven FAK cardiac-specific deletion, the use of MLC2a-Cre also leads to embryonic death at an early stage of development. At E13.5 all embryos appear normal, but at E14.5 mice show total body edema and nonspecific

focal hemorrhages associated with cardiac failure. Histological analysis shows a thinning in the myocardium, septum, and trabeculae. At E16.5 there are ventricular septa defects and thin ventricular walls along with embryonic lethality. Analysis of the tissue with electron microscopy reveals a dilation of the rough endoplasmatic reticulum, mitochondria with irregular or disrupted cristae, and thin disorganized myofibrils. At E14.5 there are also reduced numbers of mitotic cells present in the heart of the FAK cardiac-restricted mice compared with genetic and age matched mice. The few mice with cardiac specific FAK deletion that survived into adulthood are fertile and they have a normal lifespan, but examination of the heart shows eccentric right ventricle hypertrophy [61].

3.4 Cardioprotective role of FAK in the adult heart

Several studies conducted so far demonstrate that in the adult heart FAK mediates mechanical and hypertrophic signaling, and exerts a critical role in cardiac survival, adaptation, and protections of myofilament structure under conditions of stress [62–65]. Cardiac specific deletion of FAK in mice at a perinatal stage does not alter baseline cardiac function and hemodynamics [66], and there are no differences seen in the posterior and intraventricular septal wall thickness or LV chamber size [67]. However, when treated with Angiotensin (Ang) II or subjected to trans-aortic constriction (TAC), these mice develop eccentric hypertrophy associated with re-expression of skeletal-actin, Atrial Natriuretic Factor (ANF), Brain Natriuretic Peptide (BNP), beta Myosin Heavy Chain (MHC), and collagen I and VI. These mice also display increased fibrosis, but no increase in cell death. In contrast to these findings, expression of a truncated form of FAK increases the basal level of apoptosis [68]. RNA analysis shows that TAC-induced ANF expression is abolished in FAK deficient mice concomitant with an increase in alpha but not in beta MHC [67]. FAK deletion leads to disorganized myofibrils with increased interspace filled with large aggregates of swollen mitochondrial [66, 68]. Long term exposure to TAC leads to an increase in wet lung weight, decreased cardiac output, and increased interstitial fibrosis. FAK cardiac deficiency blocks ERK1/2 activation induced by adrenergic stimulation [67], and phosphorylation of both p130cas and paxillin is reduced [66, 69]. In aging mice FAK deficiency leads to spontaneous decrease of heart weight/body weight and myocyte cross-sectional area, increase thickness of LV posterior wall and fibrosis [67].

Hypertrophy induced by Angiotensin II is blocked by the expression of FRNK, a naturally occurring dominant negative isoform of FAK. In these myocytes ANP and NF-κB expression is decreased, as well as Erk1/2 and Akt basal phosphorylation [70]. Treatment with calcium chelators effectively blocks AngII induced phosphorylation of FAK, ANF expression, and decreases expression of fatty acid oxidation-related genes. Activation of the receptor PPARδ also blocks FAK-dependent activation of Erk1/2 but not of c-Jun N-terminal Kinase (JNK) [71]. In neonatal cardiomyocytes stimulation with hypertrophic agonists induces activation of FAK at S910, which can interact with paxillin and it is involved in sarcomere assembly, cell migration, and heart failure. Further analysis shows that this activation depends on Erk1/2 as well as Src/Erk5 and Protein Kinase C (PKC)δ/Erk5 [72]. FAK overexpression, in absence of other stimuli, leads to concentric hypertrophy, associated with increased heart size, β-MHC expression, and left ventricular wall thickening, without changes in the left ventricle diameter or fractional shortening. In contrast FAK

overexpression during pressure overload exerts a cardio-protective role via Akt, mTORC1, S6K, and rpS6 signaling [73]. Pressure overload alone can induce FAK activation [74] and it associates with Src, Grb2 [75], and ARHGAP21 [76, 77].

FAK also plays a critical role in linking events initiated by mechanical stress during hypertrophic responses in cardiomyocytes. Mechanical stretch activates and changes the localization of FAK, from the nucleus to the myofilament [78], as well as increasing the phosphorylation of Erk1/2, and paxillin [79, 80]. FAK accumulated in myocytes of failing hearts in spontaneously hypertensive rats [81, 82] and it is phosphorylated by integrin receptors [64, 83]. Inhibition of FAK blocks stretch-induced ANF expression [78]. In cultured Neonatal Rat Ventricular Myocytes (NRVM) FAK is associated with Shp2 and after stretch this complex is significantly reduced. Stretch reduces protein tyrosine phosphatase Shp2 phosphatese activity, and its inactivation leads to increased basal FAK phosphorylation, cell size, and expression of β-MHC [84]. Depletion of FAK with siRNA or inhibition of Src with the kinase inhibitor PP2 blocks stretch induced activation of Erk1/2, Akt S473, and S6K [84].

FAK is also involved in cardiomyocyte survival in the setting of metabolic stress including ischemic injury. In isolated NRVM chemical inhibition of glycolysis and myocardial respirationinduces phosphorylation of FAK, its association with PI3K, and Akt activity [85]. Overexpression of FAK is cardioprotective during ischemic injury by experimental myocardial infarction. FAK overexpressing mice have smaller infarct area, higher ejection fraction and fractional shortening after 8 weeks of remodeling. Further analysis shows reduced apoptosis and increased NF-κB translocation into the nucleus and transcription activity [86]. FAK cardiac restricted deletion in mice subjected to transient ligation of LAD coronary artery results in a higher infarct size and cell death, as well as in a decrease in heart function, and activation of NF-κB survival pathway [87]. Similar results were observed in mice overexpressing FRNK [85].

Stretch reduces basal phosphorylation of FAK at Y861, but it is increased with concomitant inhibition of the AngII receptor. Overexpression of FRNK or disruption of integrin β1D abolishes basal and stretch-mediated phosphorylation of FAK and ERK1/2 [88]. Tension-mediated focal adhesion maturation is a critical step for myocytes in adaptation to mechanical tension. Localization of vinculin at focal adhesion sites in myofibroblast depends on extracellular matrix stiffness and myosin II. Myosin II is also able to modulate recruitment of vinculin via FAK-dependent phosphorylation of paxillin [89].

4. ErbB/FAK/Integrin interaction

4.1 The role of Integrins in the heart

Integrins are transmembrane receptors able to sense alterations in the extracellular matrix and translate them to the cytoskeleton. They are formed by two different chains, α and β, non-covalently associated. Both subunits are present in different splicing variants (18 for α and 8 for β) leading to more than 24 possible heterodimers[90, 91]. Each splicing variant and heterodimer has a specific expression pattern, unique for tissue type and developmental stage[92–95]. Integrins can regulate the expression levels and the activation status of ion

channels, as well as initiating specific ion currents directly or through the Src tyrosine kinase signaling[96, 97]. Hormone[98, 99] and growth factor receptors[100, 101] often interact with integrins. Integrins are essential for growth factor receptors and hormone mediated cell survival[102, 103], DNA synthesis[104, 105], and chemotherapy resistance[106].

Alterations in the ECM and integrin expression have been associated with various cardiac conditions. It has been observed that accumulation of ECM components in the myocardium and coronary arteries leads to cardiac failure[107, 108]. In pressure overload, integrin receptors subtypes change, suggesting a role in mechano-transduction[109–112]. Restricted deletion of β1 in myocytes leads to myocardial fibrosis and development of spontaneous dilated cardiomyopathy in 6 month old mice, as well as an exaggerate response to pressure overload without evidences of cell death[8]. A more severe phenotype has been observed in transgenic mice overexpressing a dominant negative isoform of β1. These transgenic mice die at perinatal stage and their hearts display extensive fibrotic replacement [113].

Upon activation, integrins associate at focal adhesion sites and bind actin filaments. The interaction with actin is mediated by proteins with structural (talin and vinculin)[114, 115], signaling (Fak, Src, and PIPKγ)[116–118], and adaptor (p130CAS and melusin) functions[119–123]. One of the best characterized pathways is the Src/FAK signaling, which also promotes actin anchoring (see paragraph 3.2) [24].

4.2 Cross talk between integrins and ErbB receptors

Two different types of cross-talk between integrins and ErbB receptor tyrosine kinase (RTK) have been identified. The first is commonly called “collaborative”, where both integrins and RTK need to be activated by their respective ligand to form a cluster[124]. This interaction between RTK and integrins is mediated by FAK[44, 125]. In the second, called “direct”, integrins can directly phosphorylate RTK without the need of growth factors and FAK signaling[126, 127].

In cancer cells there is solid evidence for integrin/ErbB2 cross talk, whereas to date this has not been fully investigated in the heart. Cancer cells overexpressing both ErbB2 and integrin receptors α6β4 are highly aggressive and have a malignant phenotype[128]. In cell lines of breast carcinoma laminin induced phosphorylation of ErbB2 via integrin interaction[129]. Further analysis demonstrated that both integrins and ErbB2 co-localized[130, 131] and formed aggregates with tyrosine kinase proteins[44, 125]. These observations suggest a possible interaction between ErbB2 and integrin signaling. Expression of a constitutively active ErbB2 isoform in MFC-7 breast cancer cells leads to increase cell motility and it is associated with a higher expression of the integrin β1[132]. In human mammary and ovarian carcinoma cells the integrin receptor α6β4 co-immunoprecipitates with ErbB2. Further analysis demonstrated that upon binding to laminin α6β4 can also increase ErbB2 phosphorylation[128]. The co-activation of both receptors is required to induce PI3K activation and motility in NIH3T3 cells[124]. β4 integrin can also regulate ErbB2 dependent DNA synthesis[104] and ErbB2 translation[133], enhances ErbB2-dependendent expression of the growth factor VEGF, which in turn enhances tumour cell invasiveness[134, 135], and transactivates EGFR/ErbB2 signaling[133].

β1 integrin receptor is highly expressed in cardiomyocytes and is also the most abundant in the heart and may well interact with ErbB signaling according to literature in other cell types. Early on it was shown that in metastatic breast carcinoma cells cell adhesion is enhanced by activation of integrin β1[136]. In an epithelial tumor cell line overexpressing the ErbB2 receptor increases α5β1 expression and improves cell survival[137]. In earlier stages ErbB2 activation impairs spreading and adhesion on collagen surfaces by inactivating integrin β1 via PKB and PI3K/mTOR signaling[138, 139]. ErbB2 activation and overexpression can also induce scattering and apoptosis in human mammary epithelial cells cultured on collagen[140]. In contrast inhibition of laminin binding to integrin receptors (α6β4 or α3β1) sensitizes cancer cells toward ErbB2 specific cancer therapeutic agents Herceptin and Lapatinib[55].

In cardiac myocytes Nrg-1β induces specific phosphorylation of Src (Y215 and Y416) and FAK (Y867) and promotes the formation a protein complex between ErbB2 and Src, FAK, p130CAS, and paxillin[44]. These observations suggest the possibility of an ErbB/integrin cross-talk in cardiomyocytes. We hypothesize that the activation of FAK promotes the formation of an ErbB2/ErbB4/integrin complex, recruits and phosphorylates p130CAS, and modulates focal adhesion complex (FAC) and mechanical coupling (Fig 1). Further work will be necessary to fully explore this model in cardiac myocytes and understand the role that this plays in regulating cardiac structure and function.

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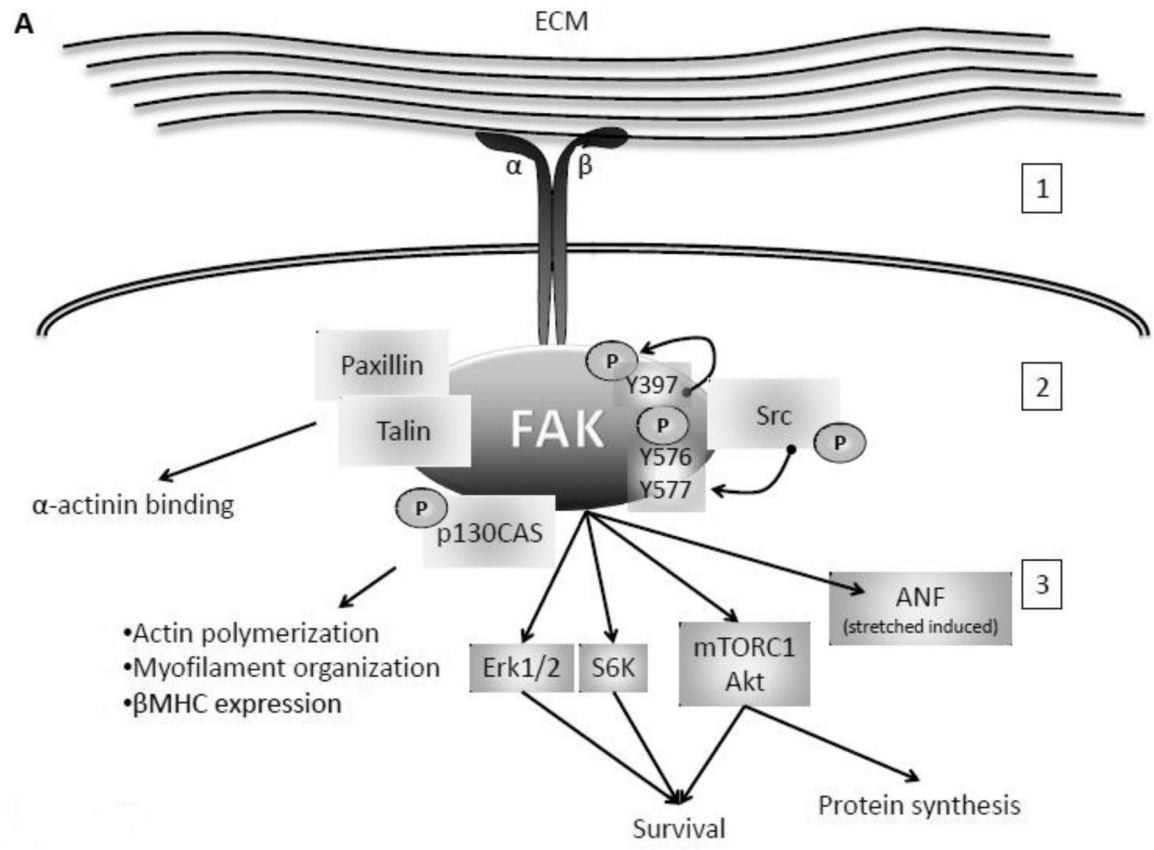
Highlights

- Nrg/ErbB signaling is critical for cardiac protection under condition of stress.
- Nrg/ErbB activates FAK signaling pathway in cardiac and cancer cells.
- FAK is critical for cardiac differentiation and survival under condition of stress.
- FAK mediated mechanical signal transduction initiated by integrins.
- These observations suggest a possible ErbB/integrin cross-talk mediated by FAK.



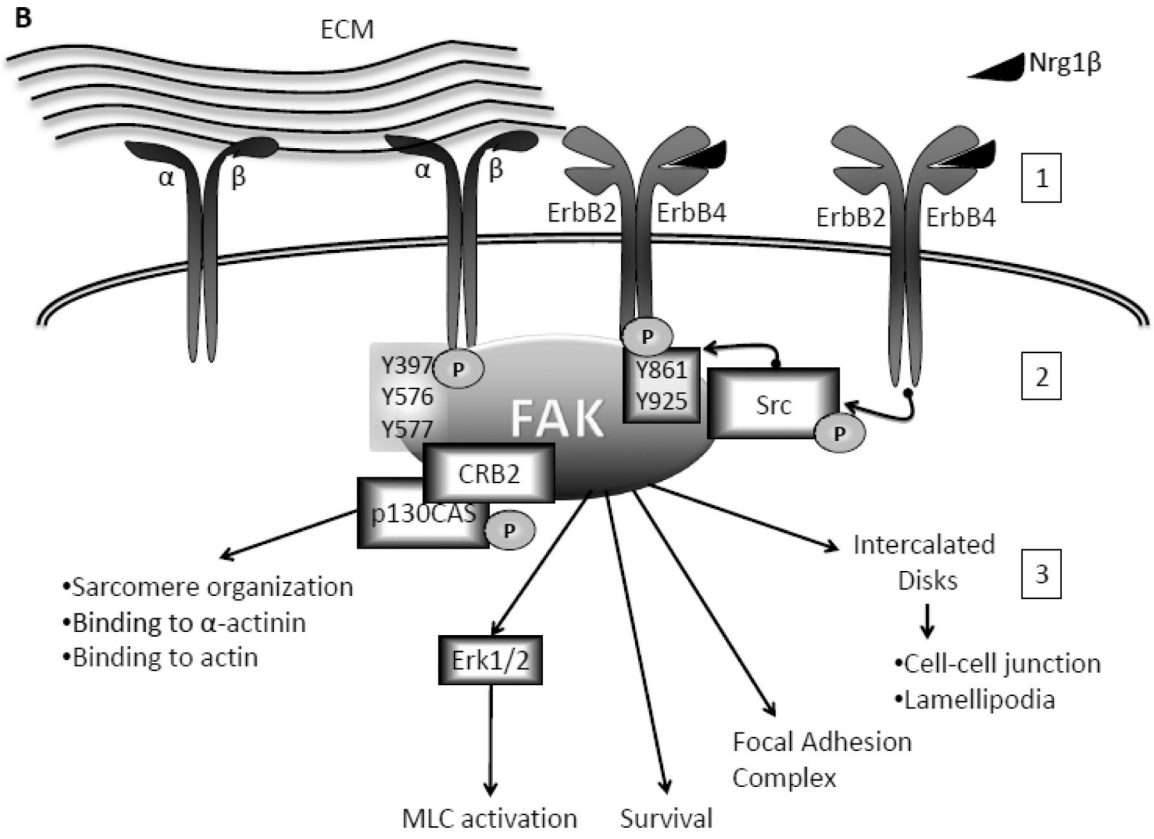


Fig 1. FAK activation and role in cardiomyocytes.

A. *Integrin-dependent activation of FAK*. Binding to the extracellular matrix (ECM) and mechanical stretch activates integrin receptors at the cell surface **(1)**. To initiate intracellular signaling integrin dimer induces conformational changes in FAK and auto-phosphorylation on tyrosine (Y) 397. Src can then phosphorylate FAK at Y576 and Y577 in the activation loop **(2)**. Activated FAK can then: interact with Paxillin and Talin to bind α-actinin; induce actin polymerization, myofilament organization, and expression of Myosine Heavy Chain (MHC) via p130CAS; and promote survival via Erk1/2, S6K, mTORC1, and Akt, protein synthesis via mTORC1 and Akt, and stretch induced expression of ANF **(3)**. **B.** *Nrg1β-specific phosphorylation of FAK and its role in cardiomyocytes*. Upon binding to Nrg1β **(1)**, the ErbB2/ErbB4 heterodimer induces phosphorylation of FAK at Y861 and Y925 via Src **(2)**. Phosphorylated FAK: is involved in sarcomere organization and binding to actin and α-actinin via interaction with p130CAS and CRB adaptor proteins; induces activation of Myosin Light Chain (MLC) via Erk1/2; promotes myocyte survival and focal adhesion complex formation; and migrates to the intercalated disks where it promotes cell-cell interaction and lamellipodia formation **(3)**.